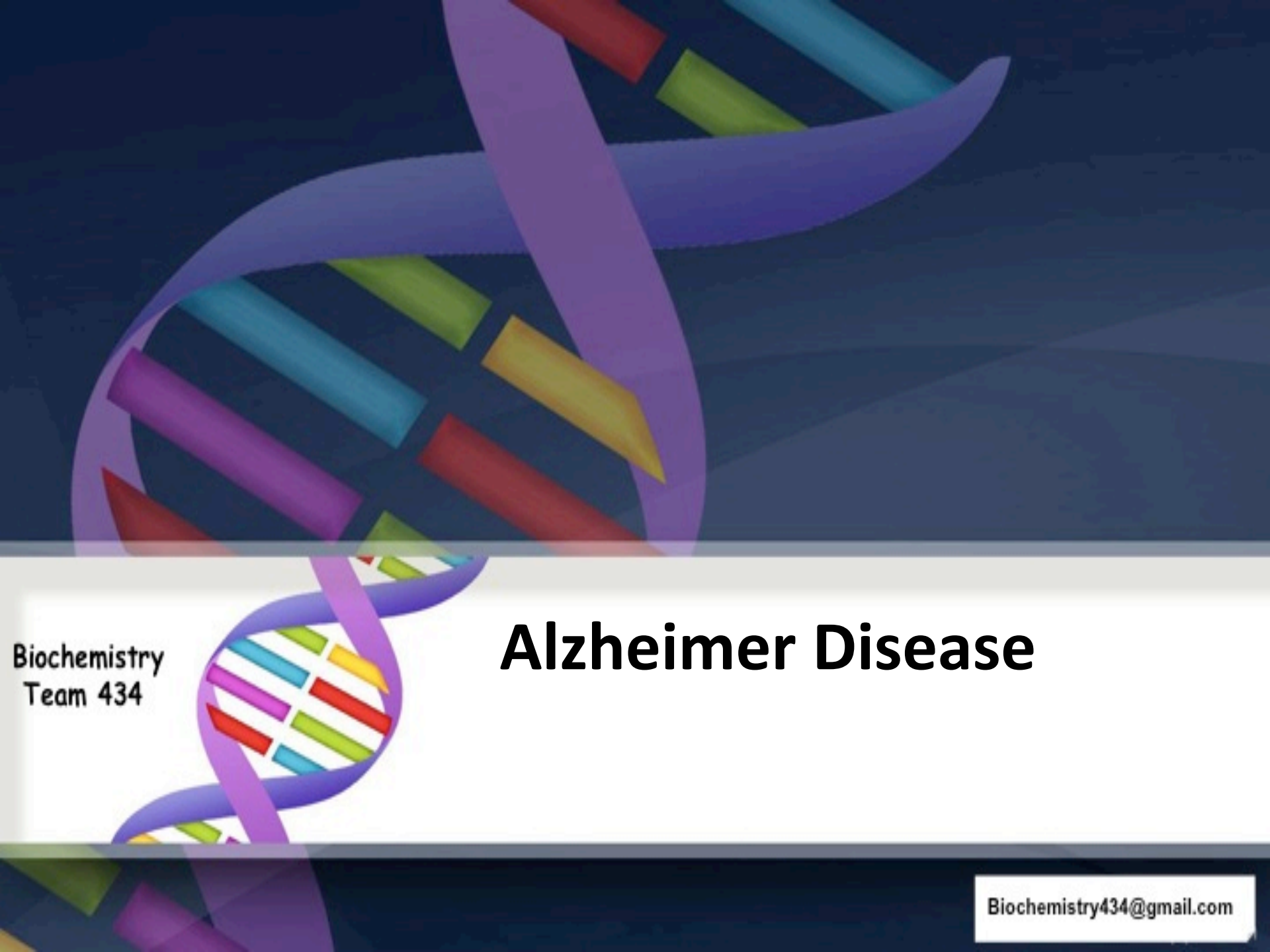

Biochemistry
Team 434

Alzheimer Disease

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Objectives

Upon completion of this lecture, the students should be able to:

-Have an overview of neurodegenerative disorders

-Understand the role of amyloid beta 40-42 residue peptide in Alzheimer's disease

-Get an idea of the diagnosis and therapeutic approaches to treat these disorders

- **Neurodegenerative Diseases:**
- 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

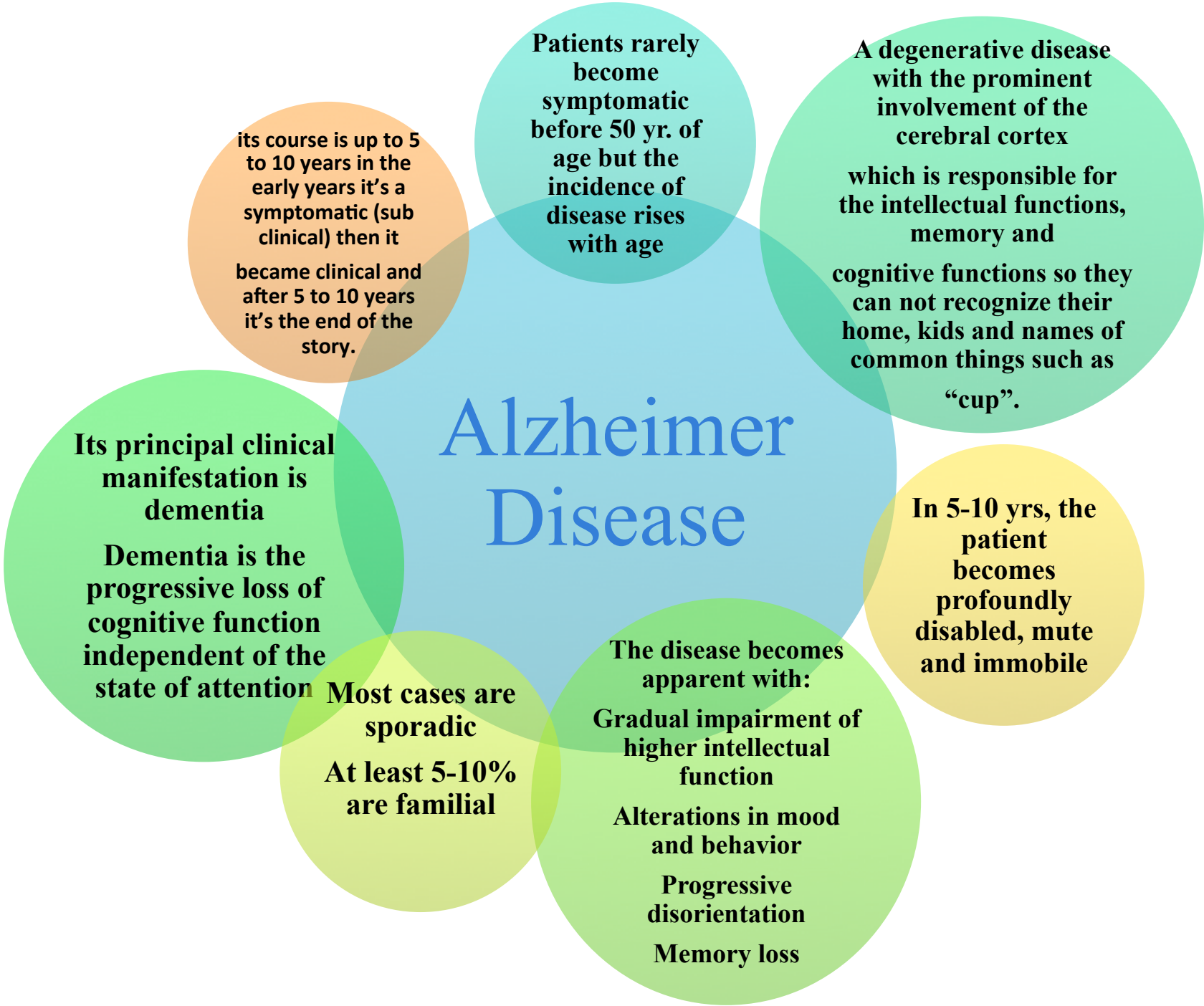
The diseases arise without any clear inciting event in patients without previous neurological deficits

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

The aggregated proteins are generally cytotoxic

Cause: is not known but it can happen to any body

typically they affect part of neurons In a specific part in the brain so this part will lose its functions especially the intellectual functions.


Alzheimer Disease
Patients rarely become symptomatic before 50 yr. of age but the incidence of disease rises with age
its course is up to 5 to 10 years in the early years it's a symptomatic (sub clinical) then it
became clinical and after 5 to 10 years it's the end of the story.
A degenerative disease with the prominent involvement of the cerebral cortex
which is responsible for the intellectual functions, memory and
cognitive functions so they can not recognize their home, kids and names of common things such as
"cup".
Its principal clinical manifestation is dementia
Dementia is the progressive loss of cognitive function independent of the state of attention
In 5-10 yrs, the patient becomes profoundly disabled, mute and immobile
Most cases are sporadic
At least 5-10% are familial
The disease becomes apparent with:
Gradual impairment of higher intellectual function
Alterations in mood and behavior
Progressive disorientation
Memory loss

Dignosis

Combination of clinical assessment and radiologic methods
Pathologic examination of brain tissue is necessary for definitive diagnosis
Major microscopic abnormalities include: neuritic plaques, neurofibrillary tangles and amyloid angiopathy

- Neuritic Plaques
- Neurofibrillary Tangles
- Amyloid Angiopathy

Neuritic Plaques :

Spherical with 20-200 μm 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)
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.
Other less abundant proteins in the plaque:

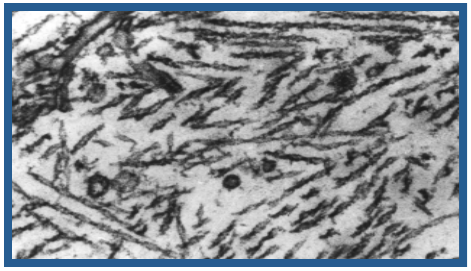
- **Components of the compliment cascade**
- **Proinflammatory cytokines**
- **α_1-Antichymotrypsin**
- **Apolipoproteins**

microscopic:1- neuritic plaques also called (senile plaques). These plaques come from a beta protein which is normally a Trans-membrane protein across the membrane

Neurofibrillary Tangles

- 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 microtubule assembly

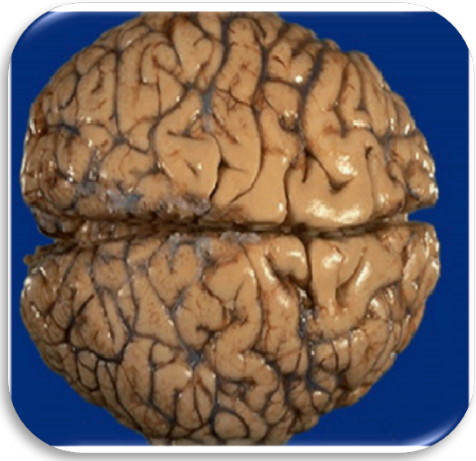
Note: The tangles are associated with symptoms but plaques aren't. but they are correlated with each other somehow plaques will appear first than tangles appear later.
So the more the tangles the more the symptoms (for example dementia) and more losses of synapses also will lead to more dementia.



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

Pathogenesis of Alzheimer's



Still being intensively studied

Strong correlation of number of neurofibrillar tangles with degree of dementia than neuritic plaques

Biochemical markers correlated to degree of dementia include:

Loss of choline acetyl transferase

Synaptophysin immunoreactivity

Amyloid burden

Loss of synapses best correlates with severity of dementia

The Aβ peptide forms β-pleated sheets and aggregates

Resistant to degradation

Elicits a response from astrocytes and microglia

Can be directly neurotoxic

Aβ Peptides

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

Aβ Peptides: in Alzheimer disease these peptides will not be cleared from the body because they became resistant to degeneration by enzymes. Why? Because it changes its structure so they become β sheaths and insoluble and they start to accumulate and become neurotoxic.

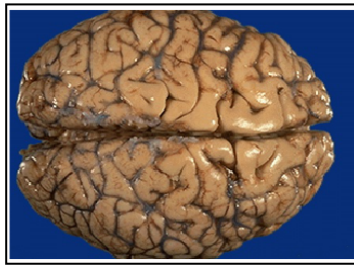
The function of Aβ protein is not clear, some says it helps in neuronal functions but it's a trans-membrane protein. Normally its cleaved by enzymes (secretases alpha, beta and gamma) into small fragments.

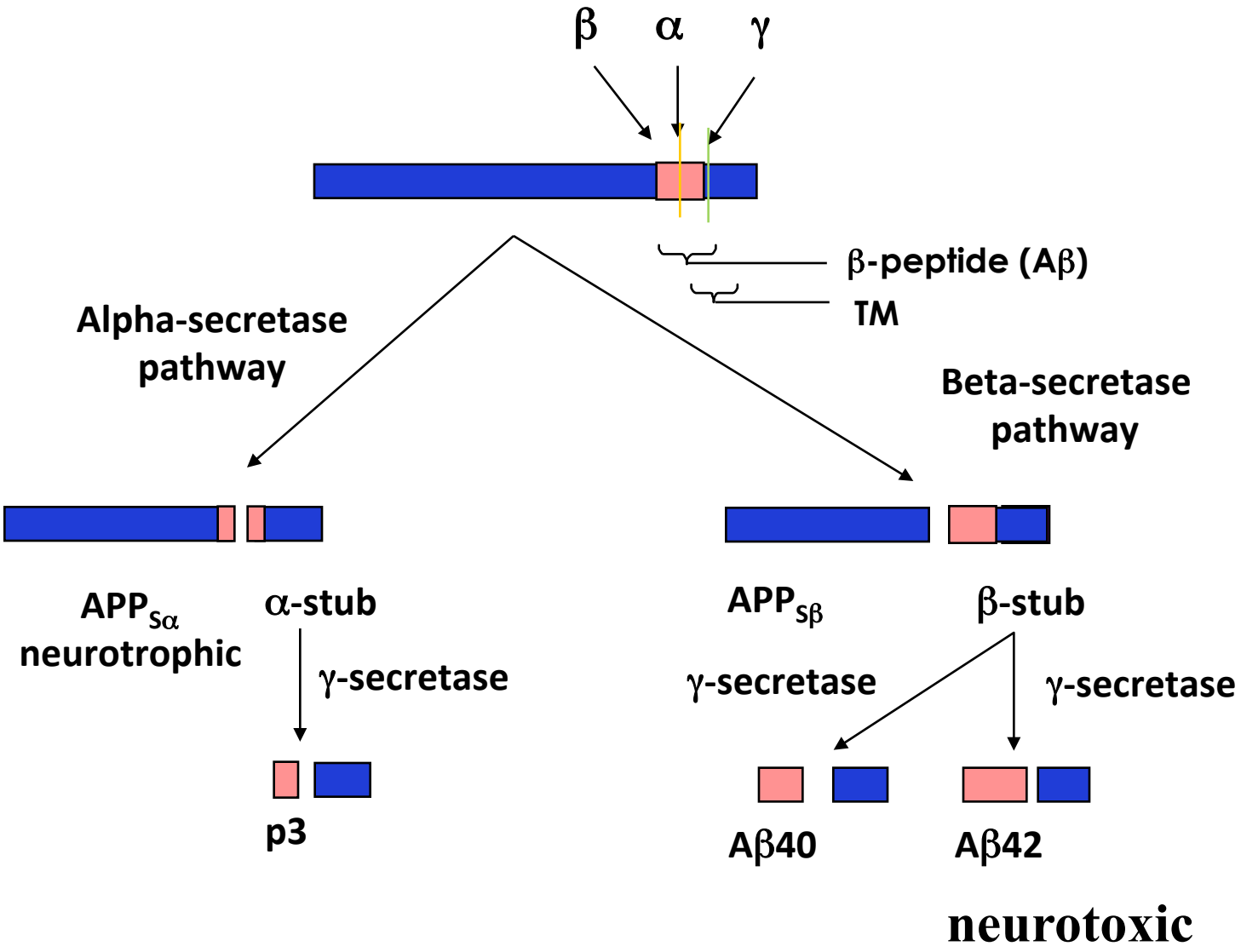
The first pathway is normal: alpha secretase enzymes start to break it into 2 fragments than gamma breaks it further more

The problem in the second pathway: that's why it is called Aβ Peptides. Beta will cut it into two fragments than comes gamma and breaks it more but abnormally it will cut it more than one cut at the wrong sides so the fragments will change their shape and they become insoluble.

The majority of abnormality is in the gamma level but it can be at beta level

Two pathways for APP processing





Mechanism of amyloid generation :

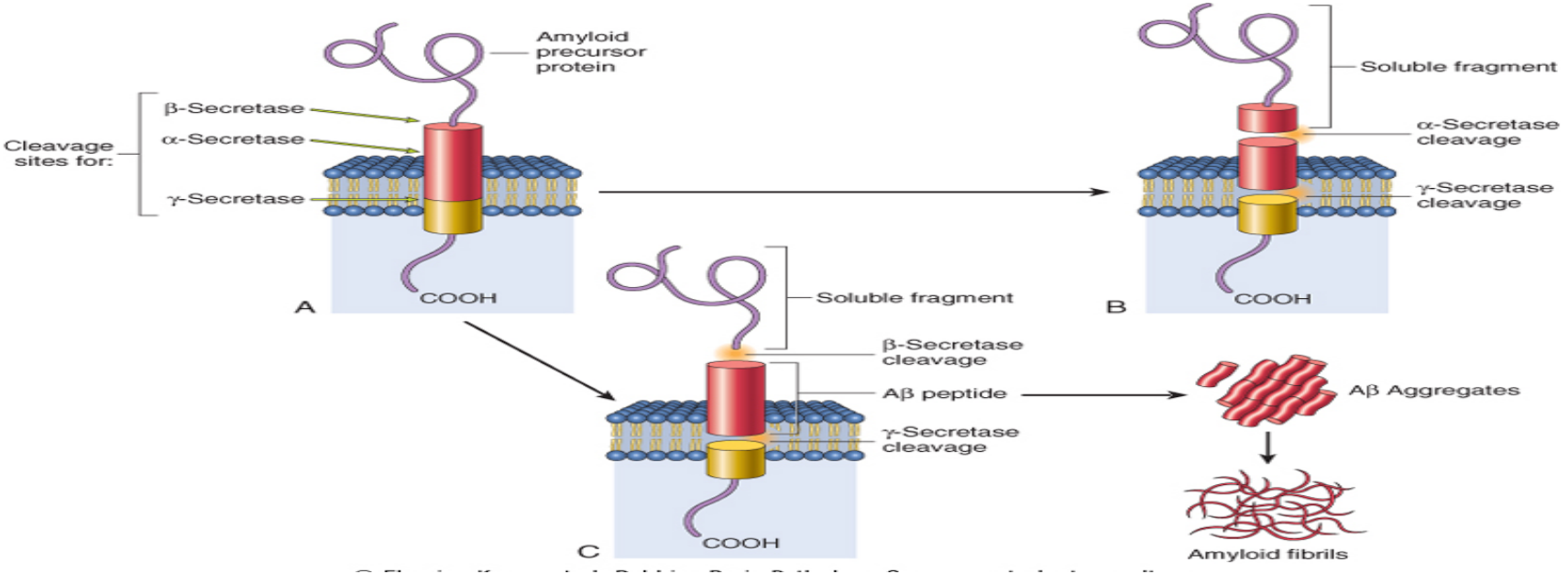
APP has potential cleavage sites for three distinct enzymes (**α, β, and γ-secretases**)

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

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

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

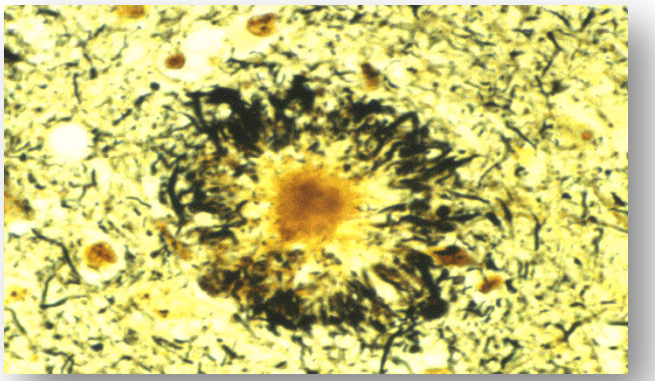
Aβ can then aggregate and form fibrils



Accumulation of Aβ protein

Accumulation of Aβ protein affects neurons and neuronal function:

- **Small aggregates of Aβ alters neurotransmission**
- **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**

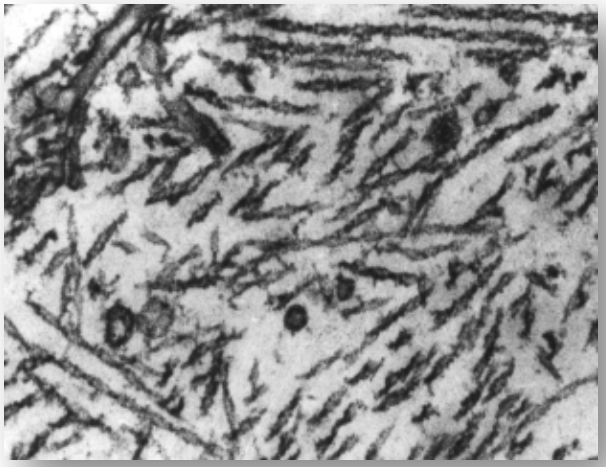


The Tau Protein

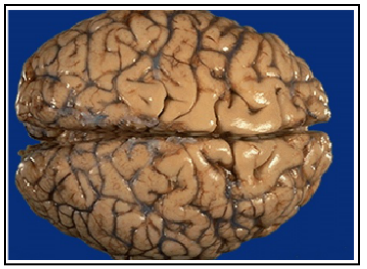
Presence of Aβ causes hyper-phosphorylation of tau protein in neurons

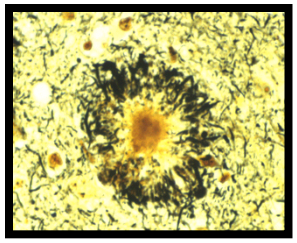
This leads to redistribution and aggregation of tau protein into tangles in neurons (from axon into dendrites and cell body)

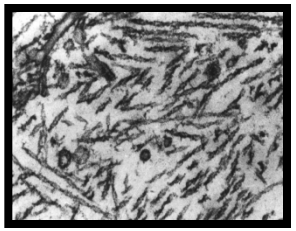
The process results in neuronal dysfunction and cell death



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







Factors that elevate Aβ → Aβ → ?? → Tau

Aβ → **Fibril assembly** → Nerve cell mis-function and death?

Tau → **Filament assembly** → Nerve cell mis-function and death?

Genetics of Alzheimer's

1- Mutations in APP gene
2- 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.
3- 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
This may provide new clues to pathogenesis of the disease

Chromosome	Gene	Consequences
21	Amyloid Precursor Protein (APP)	Early onset FAD 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)	Increased risk for development of AD Decreased age at onset of AD

Genetics of Alzheimer's: FAD: familial Alzheimer's disease and it's count for 5-10% only

Treatment of AD

Currently, no effective treatment for AD.

regulating neurotransmitter activity e.g., Enhancing cholinergic function improves AD.

they use acetylcholinestrease inhibitor to increase ACH

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.

Proinflammatory responses may be countered through polyphenols (flavonoids). Supplementation of these natural compounds may provide a new therapeutic line of approach to this brain disorder.

Cellular therapies using stem cells offer great promise for the treatment of AD

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.

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

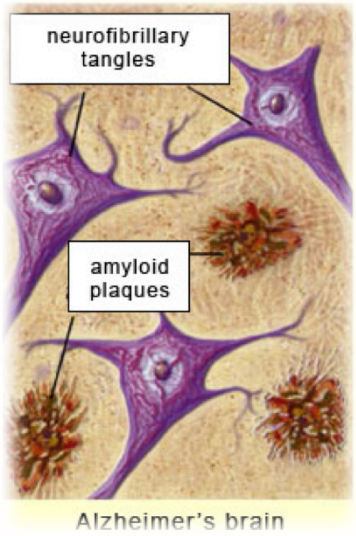
summary

DEMENTIA

Principal **clinical** manifestation

Major **microscopic** abnormalities

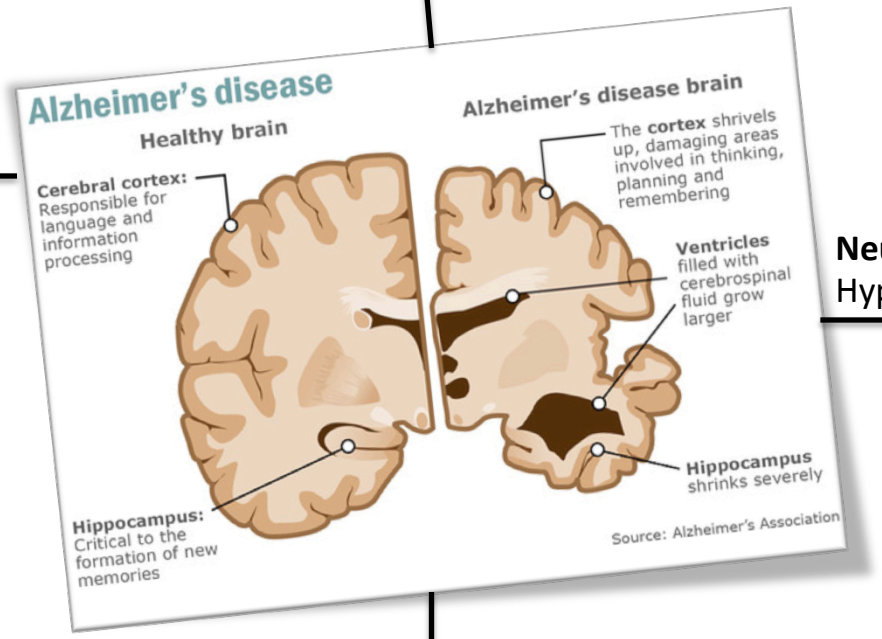
- **Neurofibrillary tangles**
- **Neuritic plaques**
- **Amyloid angiopathy**



Alzheimer's brain

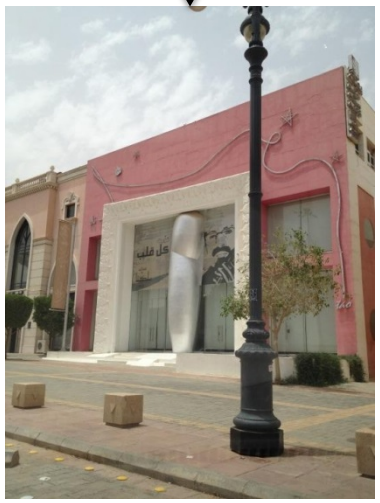
Neuritic plaque dominant component:

Aβ 42



Neurofibrillary tangles contain: Hyperphosphorylated form of

tau protein



Biochemical markers

- Loss of **choline acetyl transferase**
- Synaptophysin immunoreactivity
- Amyloid burden

MCQ

Q1: A neurodegenerative disease is a disease of the...?
A-White matter.
B-Grey matter.
C- Glial cell.
Answer: B

Q2: Alzheimer disease is a degenerative disease with prominent involvement of the ?
A- Cerebral cortex.
B- Thalamus.
C- Hypothalamus.
Answer: A

Q: 3Alzheimer principle clinical manifestation is ..?
A- Nausea
B- Dysgeusia
C- dementia
Answer: C

Q4: The major microscopic abnormalities in Alzheimer include?
A- neuritic plaques.
B- neurofibrillary tangles.
C- Both A&B
Answer: C

Q5 :In Alzheimer disease ,The dominant component of the plaque core is ..... , a peptide derived from a larger molecule called ..... ?
A- A beta , Amyloid precursor protein.
B- A gamma , Dystrophin.
C- A alpha , amyloid precursor protein.
Answer: A

Q6: The gene encoding APP is located in chromosome number .....?
A- 19.
B- 21.
C- 14
Answer: B

SAQ ..

Q1- APP has potential cleavage sites for three distinct enzymes , mention them .

1 - alpha .
2- beta .
3- gamma-secretases.

Q2- Accumulation of (A beta) protein affects neurons and neuronal function like ...

1- small aggregates of (A beta) alters neurotransmiission.
2- aggregates can be toxic to neurons and synaptic ending.
3- Larger deposits (plaques) also cause neuronal death.
4- Elicit a local inflammatory response leading to further cell injury.

Q3- The Alzheimer disease becomes apparent with.... ?

1- Gradual impairment of higher intellectual function.
2- Alterations in mood and behavior.
3- Progressive disorientation.
4- Memory loss.

http://youtu.be/NjgBnx1jVIU

http://youtube.com/watch?v=y3g4emLQ1Ic

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