# Alzheimer's Disease

**OBJECTIVES:**

- 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

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# Introduction

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

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

Its principal clinical manifestation is dementia which is is the progressive loss of cognitive function independent of the state of attention

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

In 5-10 yrs, the patient becomes profoundly disabled, mute and immobile

Most cases are sporadic.
At least 5-10% are familial

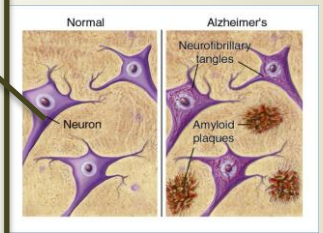
# Diagnosis

http://www.youtube.com/watch?v=dj3GGDuu15I

- Combination of clinical assessment + 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

- 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) (will discussed later)
- 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
  - α1-Antichymotrypsin
  - Apolipoproteins




## 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

## 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

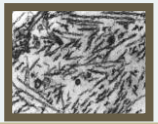
- Still being intensively studied
- Strong correlation of number of neurofibrillar tangles with degree of dementia than neuritic plaques
- Biochemical markers correlated to degree of dementia include:
  - Loss of choline acetyl transferase
  - Synaptophysin immunoreactivity
  - Amyloid burden
- Loss 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
- 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

## Aβ Peptides

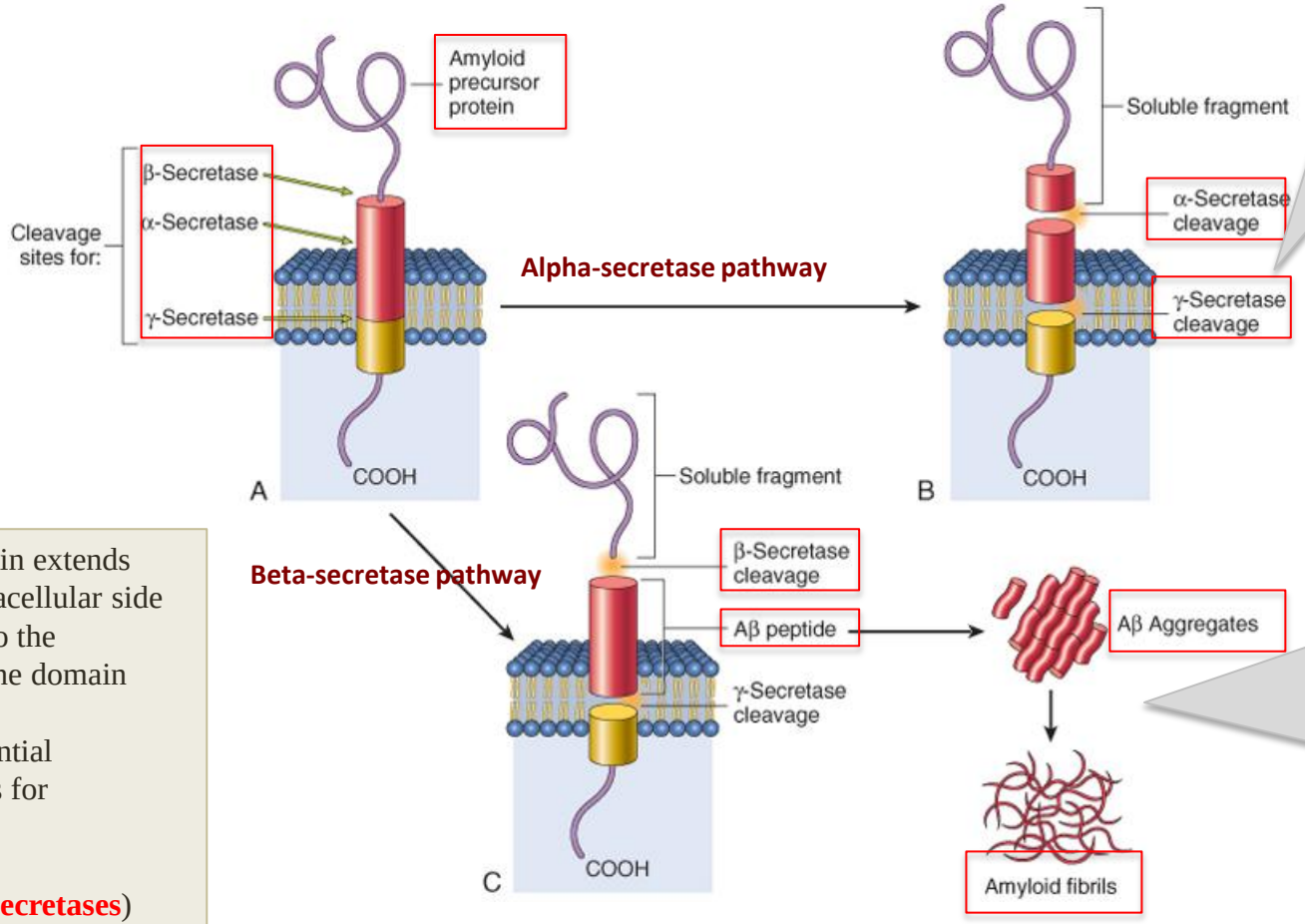
- Derived from the processing of APP
- APP is a protein of uncertain cellular function
- It is synthesized with a single transmembrane domain and expressed on the cell surface
- Aβ is a critical molecule in the pathogenesis of Alzheimer's disease

## 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



# Two pathways for APP processing




When APP is cleaved by α secretase , Subsequent cleavage by γ secretase does not yield Aβ (normal)

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-secretases**)

Mechanism of amyloid generation

**Cleavege by β-secretase followed by γ-secretase results in production of Aβ => Aβ can then aggregate and form fibrils**

# Treatment

•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.
•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 and they offer:

- ▪Cellular replacement and/or provide environmental enrichment to attenuate neurodegeneration.
- ▪Neurotrophic support to remaining cells or prevent the production or accumulation of toxic factors that harm neurons.

# Genetics

•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
•This may provide new clues to pathogenesis of the disease

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

## Research question :

- 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

1) The progression of dementia in Alzheimer's disease is strongly correlated with ?
A- Amyloid angiopathy
B- Neurofibrillary tangles.
C- Neuritic plaques.
D- Number of plaques.

2) Degradation of APP by which ONE of the following causes steps produce Aβ :
A- Cleavege by β-secretase followed by γ-secretase.
B- Cleavege by α-secretase followed by γ-secretase.
C- Cleavege by β-secretase followed by α-secretase.
D-Cleavege by β-secretase only.

3) Alzheimer's disease become apparent with:
A- Alterations in mood and behavior
B- Progressive disorientation
C- Memory loss
D- All of them.

4) A 65-years old male presented with dementia was suspected to have Alzheimer's, which of the following procedures is the best to confirm the diagnosis:
A- Brain MRI
B- Brain biopsy
C- Angiogram.
D- None of them is suitable.

5) which of the following statements is true regarding neuritic plaques ?
A- It is composed of Tau-protein.
B- It causes symptoms.
C- It has a rule in neurofibrillary tangles formation
D- It is build up in walls of arteries.

6) Which ONE of the following is more likely to have Alzheimer's diseases beyond 45 years of age:
A- Klinefelter syndrome
B- Down syndrome.
C- Color blindness
D- Edwards syndrome

7) A Brain biopsy was done to an old man who has been suffering from dementia for a long time, the lesions are more likely to be seen at:
A- The cerebral cortex
B- The cingulate gyrus
C- Corpus callosum
D- The insula.

8) The common role of Tau-protein is to :
A- Degradate Beta amyloid protein.
B- Phosphorylate other enzymes
C- Destruct the neural density .
D- Enhances microtubule assembly

1B 2)A 3)D 4C 5)C 6)B 7)A 8)D

# Thank You!

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