[lecture 4]

Alzheimer's Disease

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Teams

The Objectives

- An overview of Neurodegenerative diseases.
- The role of Amyloid $A\beta_{40}$ and $A\beta_{42}$ residue peptide in Alzheimer's disease.
- The diagnostic and therapeutic approaches to treat these diseases.

Red = Import-ant

Blue = explain

Green = addition notes

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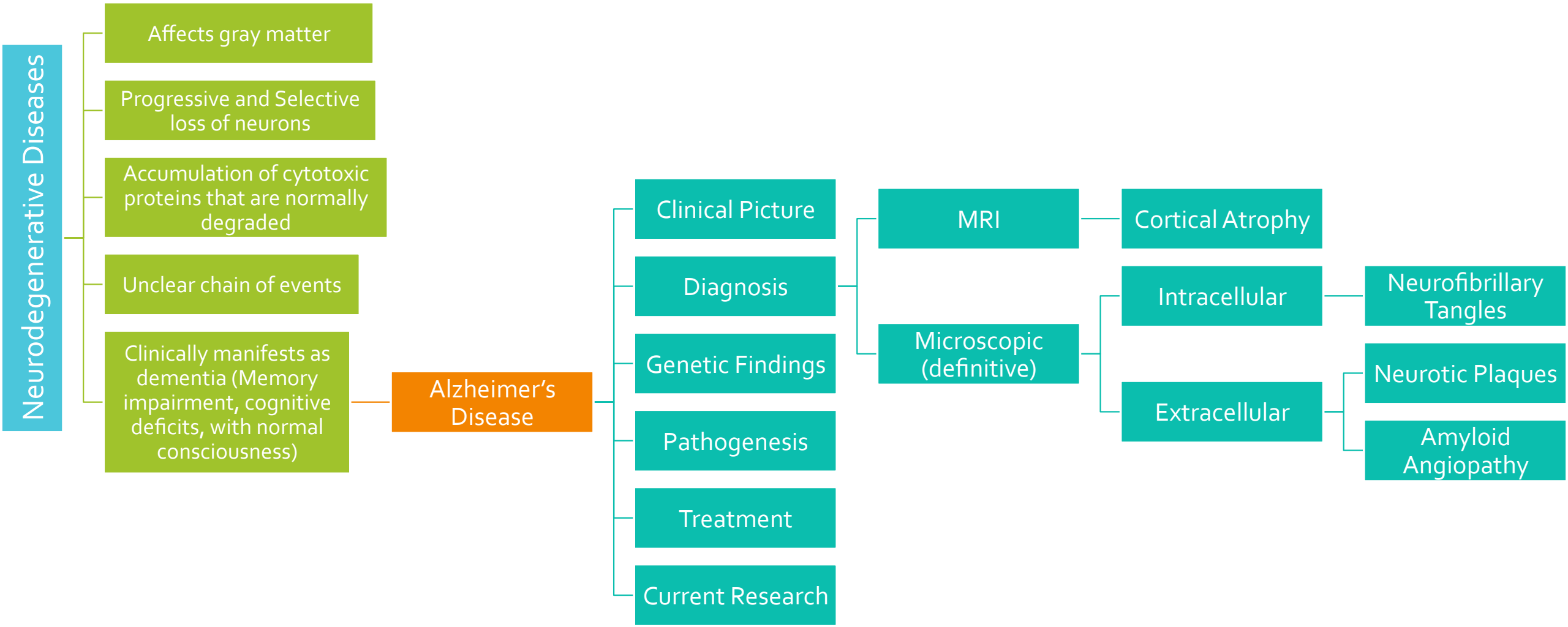
Mind Map


Neurodegenerative Diseases
Affects gray matter
Progressive and Selective loss of neurons
Accumulation of cytotoxic proteins that are normally degraded
Unclear chain of events
Clinically manifests as dementia (Memory impairment, cognitive deficits, with normal consciousness)
Alzheimer's Disease
Clinical Picture
Diagnosis
Genetic Findings
Pathogenesis
Treatment
Current Research
MRI
Cortical Atrophy
Microscopic (definitive)
Intracellular
Neurofibrillary Tangles
Extracellular
Neurotic Plaques
Amyloid Angiopathy

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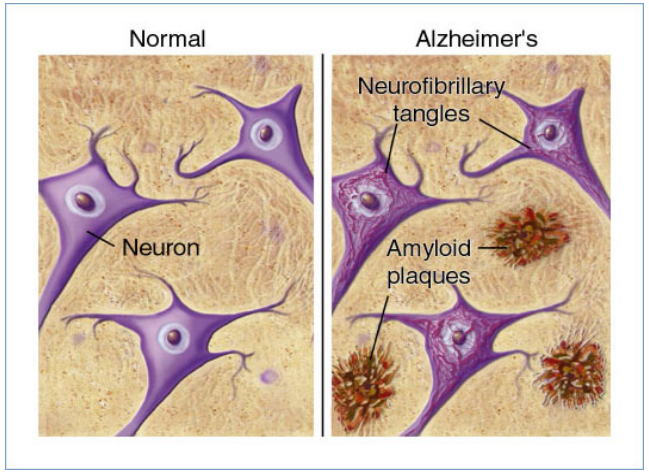
Alzheimer's Disease:

- Degenerative disease.
- Prominent involvement of the cerebral cortex.
- Incidence rises with age (rarely before 50).
- Most causes are sporadic, only 5-10% are familial (early onset and gene related).



The Clinical Picture: Dementia

1. Gradual impairment of higher intellectual functions.
2. Memory loss and progressive disorientation.
3. Alterations in mood and behavior.
4. Patient becomes disabled, mute and immobile in 5-10 years (after diagnosis).
5. Death from recurrent upper respiratory tract infections.

Diagnosis

- By a combination of Clinical assessment and Radiologic methods.
- Definitive diagnosis depends on pathologic examination of brain tissue (Microscopic abnormalities: neuritic plaques, neurofibrillary tangles, and amyloid angiopathy).

Microscopic Findings

Intracellular

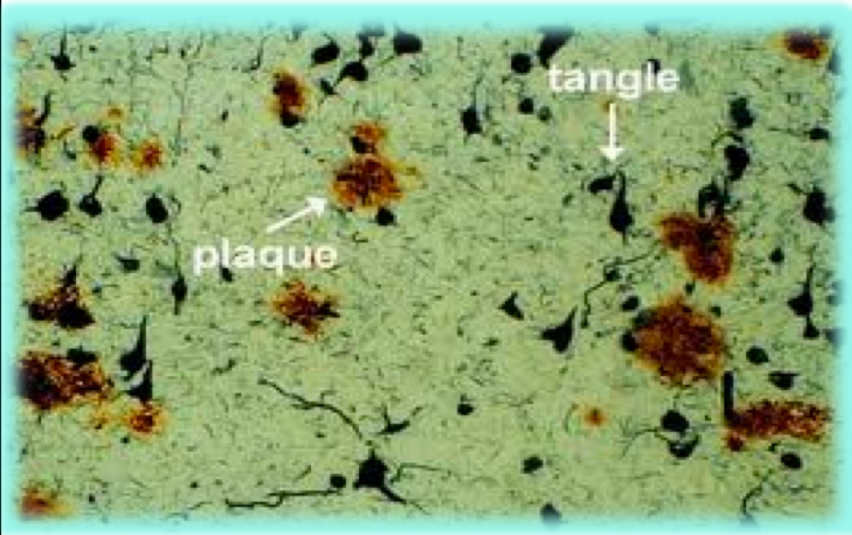
Neurofibrillary Tangles

Bundles of filaments in the cytoplasm, displacing or encircling the nucleus.

Components:

Abnormally hyperphosphorylated protein tau.

*Normally, tau protein binds to microtubules to facilitate cellular transport. When tau is hyperphosphorylated, it becomes unable to bind to microtubules. So, it accumulates forming tangles)



Extracellular

Neurotic Plaques

Spherical structures (20-200 µm in diameter).

Components:

- Paired helical structures
- Synaptic vesicles
- Abnormal mitochondria
- Many abnormal proteins at the the amyloid core, the dominant is Aβ (a peptide derived from Amyloid Precursor Protein (APP)).

Abnormal proteins:

- $A\beta_{40}$ and $A\beta_{42}$ (Same N-terminus, different number of amino acids. One is 40 and the other is 42)
- Components of the compliment system
- Proinflammatory cytokines
- α_1-antichymotrypsin
- Apolipoproteins

Amyloid Angiopathy

Accumulation of Amyloid protein on the walls of the arteries of the brain.

Components:

Amyloid protein.

- Increases the risk of stroke and dementia.
- Not specific for Alzhiemer's.

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Pathogenesis

- Still being intensively studied.
- The number of neurofibrillar tangles correlates better with the degree of dementia than does the number of neuritic plaques.

Aβ is a critical molecule in the pathogenesis of Alzheimer disease

The Aβ peptide forms β-pleated sheets, aggregates readily and is resistant to degradation and elicits an inflammatory response from astrocytes and microglia and can be directly neurotoxic.

- Are derived through the processing of APP*(is a protein of uncertain cellular function).
- It is synthesized with a single transmembrane domain and expressed on the cell surface (extracellular side).

*APP= Amyloid precursor protein

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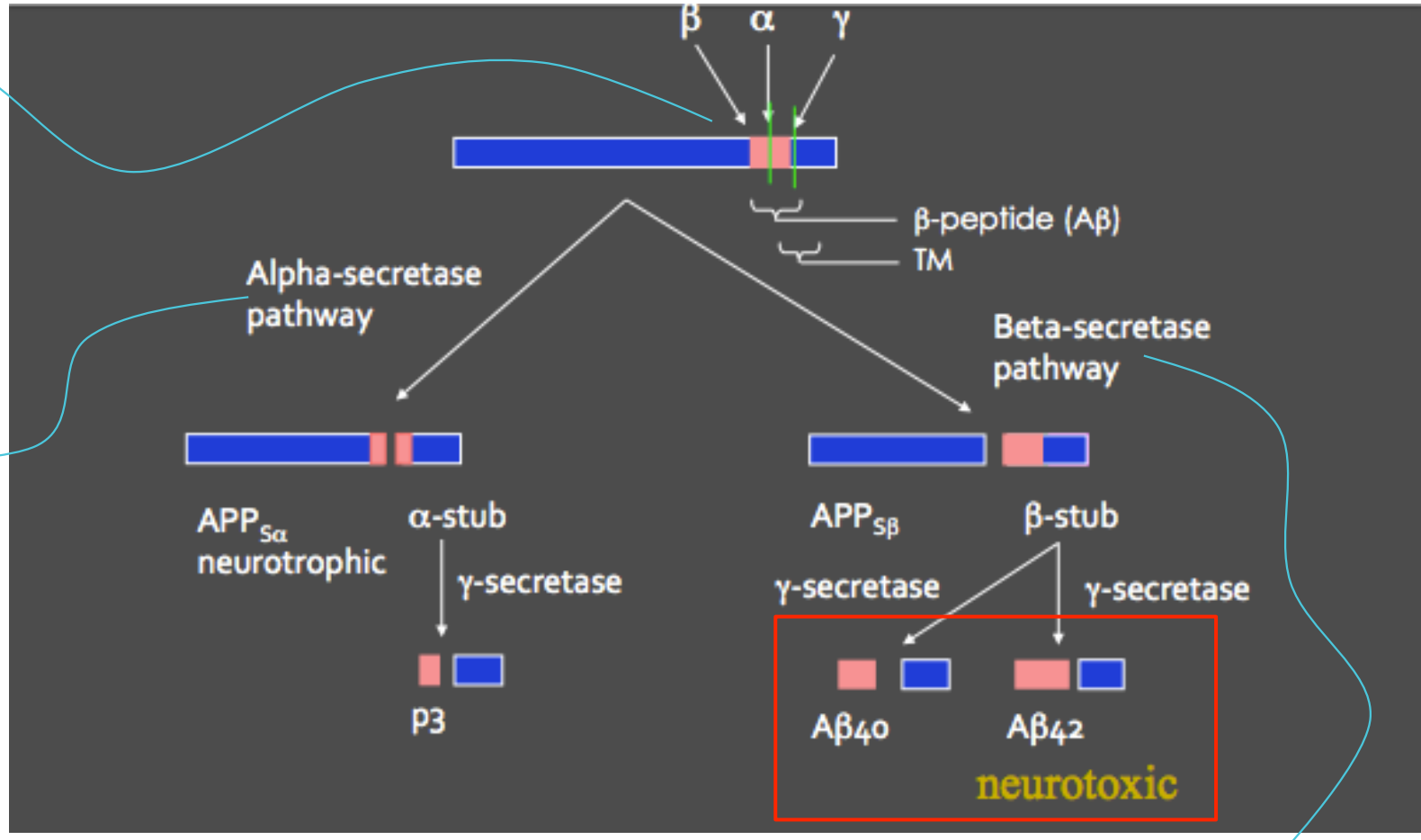
Two pathways for APP processing

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

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



Cleavage by β -secretase , followed by γ-secretase results in production of Aβ*.

Aβ can then aggregate and form fibrils

*Aβ can then aggregate and form fibrils

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Accumulation of Aβ

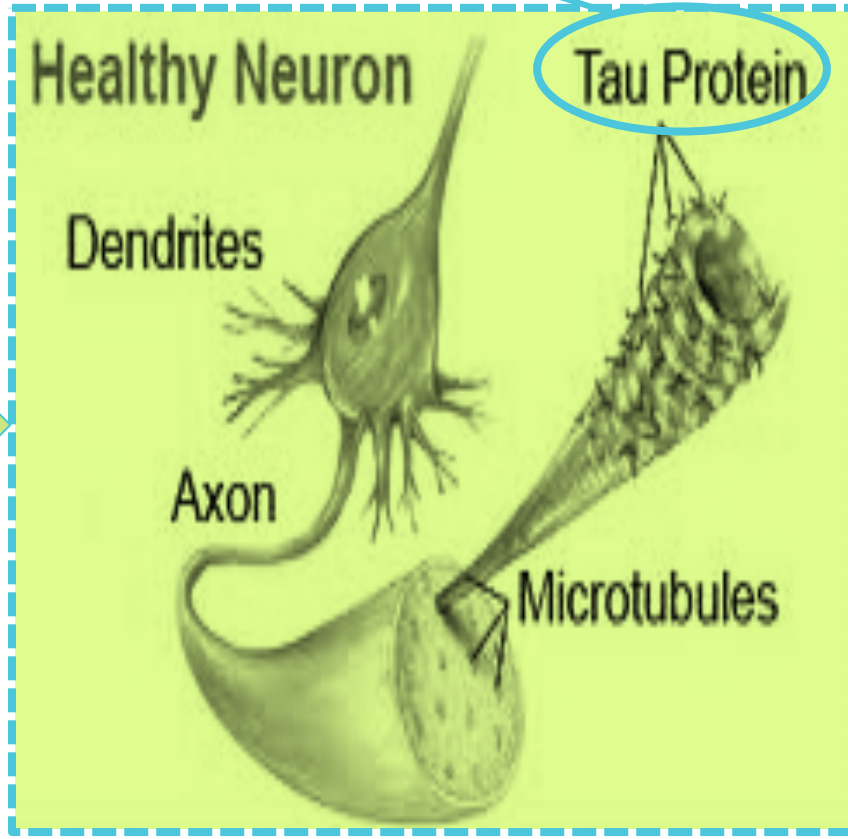
Accumulation of Aβ has several effects on neurons and neuronal function:

- ✧ **Small aggregates** of Aβ can alter **neurotransmission**, and the aggregates can be toxic to neurons and synaptic endings.
- ✧ **Larger deposits**, in the form of **plaques**, also lead to neuronal death, elicit a local inflammatory response that can result in further cell injury.

Tau Protein

Hyperphosphorylation of the microtubule binding protein "tau"

- With this increased level of phosphorylation, tau redistributes within the neuron from the axon into dendrites and cell body and aggregates into tangles.
- This process also results in neuronal dysfunction and cell death.



Genetics of AD

* Mutations in APP or in components of γ-secretase (presenilin-1 or presenilin-2) lead to early onset familial Alzheimer disease by increasing the rate at which Aβ accumulates.

**Alzheimer disease occurs in almost all patients with trisomy 21 (Down syndrome) who survive beyond 45 years (due to APP gene dosage effects).
The gene encoding APP is located on chromosome 21

***The search for genes associated with typical, sporadic Alzheimer disease is beginning to identify genetic associations that may provide new clues about the 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

Treatment of AD

- 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) (they scavenge the free radical so they prevent the oxidative damage).
- Supplementation of these natural compounds like-green tea 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.

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Continued Research of AD & Summary

- The small aggregates of Aβ as well as larger fibrils are directly neurotoxic.

- They can elicit oxidative damage and alterations in calcium homeostasis.

- But how Aβ is related to neurodegenration of AD and how it is linked to tangles and hyperphosphorylation of tau all remain open questions.

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Summary

- Neurodegeneration is the progressive loss of structure or function of neurons, including death of neurons.
- Alzheimer disease is degenerative disease with the prominent involvement of the gray matter cerebral cortex.
- Most of Alzheimer cases are sporadic.
- The major microscopic abnormalities of Alzheimer disease are neuritic plaques, neurofibrillary tangles, and amyloid angiopathy.
- Extracellular deposition of insoluble fibrous aggregates known as amyloid in certain areas of neural tissue.
- The deposition of amyloid interferes with normal cellular function, resulting in cell death and eventual organ failure.
- Aβ is a critical molecule in the pathogenesis of Alzheimer disease.
- The dominant component of amyloid plaque that accumulates in Alzheimer disease is amyloid β 42(Aβ42) Peptide.
- The number of neurofibrillar tangles correlates better with the degree of dementia than does the number of neuritic plaques.

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Test your knowledge

1-The gene encoding APP is located on :

A. Chromosome 21
B. Chromosome 18
C. Chromosome 12
D. Chromosome 20

2-Alzheimer is a degenerative disease with the prominent involvement of :

A. Spinal cord
B. Peripheral neurons
C. The cerebral cortex
D. Neuromuscular junction

3-Which of following microscopic abnormality is not specific for Alzheimer disease?

a) Neuritic plaques
b) Amyloid angiopathy
c) Neurofibrillary tangles

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Test your knowledge

4- An 80-year-old man presented with impairment of higher intellectual function and alterations in mood and behavior. his family reported progressive disorientation and memory loss over the last 6 months. there is no foamy history of dementia. the patient was tentatively diagnosed with alzheimer disease. which one of the following best describes the disease?

a- It is associated with the accumulation of amyloid precursor protein.
b- It is associated with the deposition of neurotic amyloid peptide aggregates.
c- It is associated with beta amyloid an abnormal protein with altered amino acid sequence.

Answers :

4-B 3-B 2-C 1-A

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If you find any mistake, please contact us:)

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