Alzheimer's Disease

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.**
Alzheimer's Disease overview	**1-Patients rarely become symptomatic before 50 yr. of age but the incidence of disease rises with age** **2-Most cases are sporadic.** **3-In 5-10 years, the patient becomes profoundly disabled, mute and immobile.** **4-At least 5-10% are familial.** **5-Its principal clinical manifestation is dementia** **6-A degenerative disease with the prominent involvement of the cerebral cortex.**

The disease becomes apparent with

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

Diagnosis of Alzheimer's Disease

-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

-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)
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
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 of Alzheimer's

- Still being intensively studied
- Strong correlation of number of neurofibrillary tangles with degree of dementia than neuritic plaques
- Biochemical markers correlated to degree of dementia include:
  - Loss of choline acetyltransferase
  - 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 is a critical molecule in the pathogenesis of Alzheimer's disease

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

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

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 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

Treatment of AD	▪ Currently no effective treatment for AD ▪ Regulating neurotransmitter activity (enhancing cholinergic function improves symptoms) ▪ Epidemiology shows NSAIDs decrease the risk for developing AD. ▪ Clinical trials of NSAIDs in AD patients are not very fruitful. ▪ Polyphenols such as flavonoids reduce proinflammatory responses ▪ Flavonoid supplements may be a new therapeutic approach for AD Stem cell therapy offers: ▪ Cellular replacement and/or provide environmental enrichment to attenuate neurodegeneration ▪ Neurotrophic support to remaining cells ▪ 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

Genetics of Alzheimer's

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