Overview

- History
- Signs
- Risk Factors
- Genetics of Alzheimer’s Disease
- Treatment
History

• Accounts of Dementia in Greek and Medieval History
• 1906 - Alois Alzheimer 1st defined
• 1960’s – Blessed, Tomlinson, Roth
• Pre 1970 – Focus on Acetylcholine
• 1970’s on – realization of heterogeneity
Signs of Alzheimer’s Disease

- Innocent absent mindedness
- Trouble following complex discussions
- Altered behavior: paranoia, delusions, loss of social appropriateness
- Ultimately dependent on others
Alzheimer’s Disease (AD)

- 4 million Americans suffer
- Estimated 22 million cases in 2025
- Increase in Frequency with age
- Major Public Health Concern
Risk Factors

• Serious head injury
• Poor early childhood education
• Aluminum in drinking water
Hallmarks of the Disease

• Death of Cholinergic Neurons
• Protein Clusters in the Brain (Two Forms)
  - Neurofibrillary Tangles
  - Amyloid Plaques
• Plaques present in most elderly
Affected Areas

- Language
- Memory
- Intelligence, judgement, and behavior
In PET scans a normal brain (right) shows much greater activity (yellow) than one affected by Alzheimer's disease (left).
Neurofibrillary Tangles

- Found inside nerve cells
- Formed by Tau protein

- Tau binds tubulin
- Phosphorylated by variety of kinases
- Density related to severity of dementia
Amyloid Plaques

- Appear long before Neurofibrillary tangles
- Found in extracellular environment
- Aggregation of β-AP peptide fragment
- 40 or 42 amino acids long
- Usually accompanied by Microglia
- β-Amyloid (β-AP) originates from longer peptide called β-Amyloid Precursor Protein (β-APP)
Effects of the Aβ

- Form dense plaques in hippocampus and cortex
- Increases Choline transport across nerve cell membrane
- Studies show that Aβ
  a) disrupts Ca\(^{+2}\) Regulation
  b) May damage mitochondria
β-Amyloid Precursor Protein

- Present in many cells and tissues
- 695-770 amino acids long
- Normal function β-APP unknown
- β-AP arises from cleavage of β-APP protein
- Found on Chromosome 21
- APP conserved in evolution
**β-APP**

- Transmembrane Peptide
- β-APP cut by one of two mechanisms
  1) Cleavage by α-secretase, then by γ-secretase
  2) Cleavage by β-secretase into C99-βAPP, then by γ-secretase
Extracellular

Aggregation of 42 aa peptide

Intracellular
Plaques and Tangles

Amyloid Plaques

Tau Tangles
Types of AD

• Familial (FAD)
  – Early onset

• Sporadic
  – Late onset
Genetics of AD

- **Early onset**
  - Alterations in β-APP
    - Missense Mutation
    - Increase in β-APP gene dosage
  - Missense mutation in Presenilin
- **Late onset**
  - Presence of Apolipoprotein E ε4 allele
  - α-2 Macroglobulin gene mutation
β-APP Mutations linked to AD
Presenilin mutations

- Cause earliest and most aggressive form of AD
- Presenilins part of multi-protein complexes
Apolipoprotein E

- Movement and distribution of Cholesterol
- 3 major types: ApoE2, ApoE3, and ApoE4
- ApoE2 may prevent AD
- Increased risk of AD with ApoE4
- Greater deposits of Aβ with E4
Possible ApoE4 Mechanism
Alpha 2 Macroglobulin

- Protease
- Leads to increase accumulation of Aβ
- Mutation present in 30% population
- Increases risk for late onset
<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene Defect</th>
<th>Phenotype</th>
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<tr>
<td>21</td>
<td>β-APP mutations</td>
<td>↑ Production of all Aβ peptides or Aβ_{40} peptides</td>
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<td>19</td>
<td>ApoE4 polymorphism</td>
<td>↑ Density of Aβ plaques and vascular deposits</td>
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<td>14</td>
<td>Presenilin 1 mutations</td>
<td>↑ Production of Aβ_{42} peptides</td>
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<tr>
<td>1</td>
<td>Presenilin 2 mutation</td>
<td>↑ Production of Aβ_{42} peptides</td>
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</tbody>
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β-APP, β-amyloid precursor protein; Aβ, amyloid β-protein.
Chromosome 1

Chromosome 14

Chromosome 19

Chromosome 21

PS-1

APOE

APP
Potential Therapeutic Strategies

- AChE inhibitors
- Inhibitors of Aβ production
- Use of small molecules that bind Aβ
- Administration of anti-inflammatory drugs
- Aβ Vaccine
References

- [http://www.gbhap.com/magazines/neuroscience/3-5-focus.htm](http://www.gbhap.com/magazines/neuroscience/3-5-focus.htm)
- [http://www.uku.fi/neuro/44the.htm](http://www.uku.fi/neuro/44the.htm)
Presenilin

- Presenilin 1 – Chromosome 14q
- Presenilin 2 – Chromosome 1