Alzheimer’s Disease:
A look into the Genetics, the Pathophysiology and the Future

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Alois Alzheimer and his patient Auguste D
"Numerous miliary foci are found in the superior layers. They are determined by the storage of a peculiar material on the cortex" and "in the center of an otherwise normal cell...a tangled bunch of fibrils"
What’s the Impact?
Now 4.5 million → 2050 13.8 million
Goals of the presentation

• To get a better understanding of the genetics involved in Alzheimer’s disease
• To get a better understanding of the pathophysiology and evolution of this disease over time through the use of biomarkers
• To review our current treatments
• To glimpse into what treatments we may see in the future
Genetics and Inheritance: Early Onset and Late Onset
Genetics and Inheritance

Early Onset AD

- Familial EOAD
  - APP mutation, chromosome 21
  - PS1 mutation, chromosome 14
  - PS2 mutation, chromosome 1

- Non familial EOAD
  - Unknown genes

• Early onset AD follows a Mendelian autosomal dominant pattern of inheritance
What’s the deal with amyloid?

Healthy synapse

Unhealthy synapse
Inheritance and Genetics

Late Onset AD

• Associated with many different genes
• Most strongly associated with ApoE found on chromosome 19
  – Three different alleles: ApoE 2, 3 and 4
  – We get one allele from each of our parents
  – ApoE 4 is most strongly associated with the development of LOAD
## Genetics and Inheritance

- Late onset AD

### % of those with AD by 80yo

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<th>Alleles</th>
<th>Risk</th>
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<tbody>
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Modifiable Risk Factors?
Epigenetics!
Gross Pathology
Amyloid Cascade Hypothesis
Beta Amyloid

- Increased production in familial early onset AD
- Destruction of neurons
  - Oxidative stress
  - Calcium deregulation $\rightarrow$ excitotoxicity
  - Directly neurotoxic
  - May increase production of hyperphosphorylated Tau protein
How do the LOAD genes fit into this hypothesis?

- They too promote increased production of beta amyloid
- They inhibit the reuptake and clearance across the BBB of beta amyloid
- They play a role in mediating inflammation particularly through the complement system
- They regulate lipid and cholesterol transport
Role of ApoE

- Cholesterol transporter
- Role in neuroplasticity
- Binds and can clear away beta amyloid
- Mediates inflammation

Biomarkers!

(Both imaging and CSF studies)

It is from studies like these that we are starting to develop a time frame to this disease!

Figure 5  Model of how the different stages of Alzheimer’s disease may be detected by changes in various biological, cognitive and clinical markers (from Sperling et al.⁵). CSF, cerebrospinal fluid; FDG, ¹⁸F-fluorodeoxyglucose; fMRI, functional Magnetic Resonance Imaging; MCI, mild cognitive impairment; PET, positron emission tomography.
Imaging in AD

- MRI, FDG-PET, Beta amyloid tracer PET
Imaging

- Usually not covered by insurance
- Currently most use is for research but can be helpful in clinically difficult cases
- New radionucleotides that bind only to tau are currently in the process of development
So what do we do?

Treatment:

• Right now the mainstay of treatment is with acetylcholinesterase inhibitors and NMDA receptor antagonists.
Acetylcholine and Memory

• Loss of Cholinergic cells and Acetylcholine transferase in AD patients
• Antimuscarinic drugs can cause amnesia
• Physostigmine enhances cognition
• Mice models
• Positive effects in those with AD
• Decreased phosphorylation of tau protein
NMDA receptors

- Receptor stimulation is pertinent in memory formation...
- Why in the world do we ANTAGONIZE this process in patients with AD?
Current recommended treatments
Treatment

• Study done at St. Louis University showed improved outcomes if patients were on combination therapy compared to donepizil alone

• What about starting treatment in the MCI stage?

• Article published by Baylor: what if we try to alleviate demented patients’ delirium in the hospital by starting an AchE-I?
Other treatments?

- Vitamin E
- Estrogen
- NSAIDS
- Statins
  - A randomized, double-blinded, placebo controlled trial of simvastatin to treat AD
  - 40mg daily given to those with mild to moderate AD
  - No significant effect was found compared to control
Other treatments?
The Future

Alzheimer’s Disease vs Alzheimer’s Dementia
The future

• Current drug that is in phase III clinical trials is Solanezumab, a monoclonal antibody to beta amyloid.
• It is being given to those with mild AD (in contrast to a failed drug, Bapineuzumab, of the same class, but given to those with mild to moderate dementia)
• It’s safety profile is good, compared to a previous trial for an AD vaccination that resulted in 6% of subjects contracting aseptic meningitis
• Currently banking on the fact that the amyloid cascade hypothesis is correct
• So far our biomarkers are showing early formation of beta amyloid as the first step in the pathophysiologic cascade
The Future

Alzheimer’s Disease vs Alzheimer’s Dementia
I believe in hope for a cure.
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