Alzheimer's Disease

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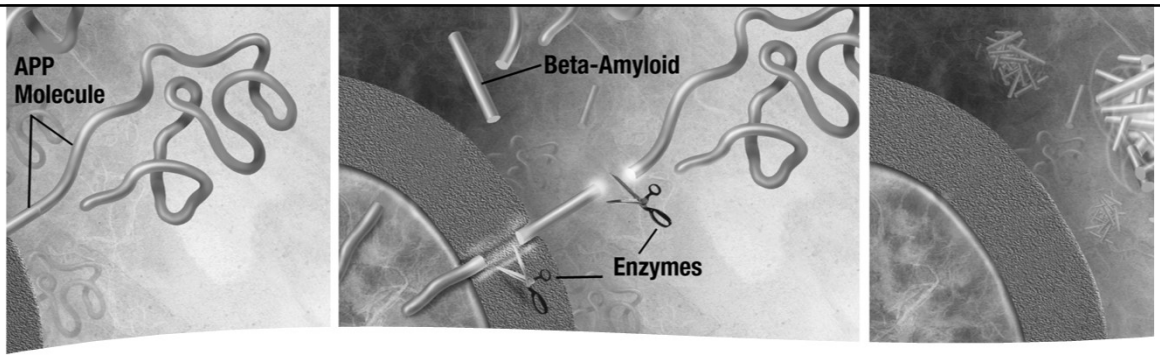
Objectives

- Describe Alzheimer's Disease pathology
- Discuss current medication options
- Highlight Alzheimer's Biomarkers
- Future directions in diagnosis and treatment

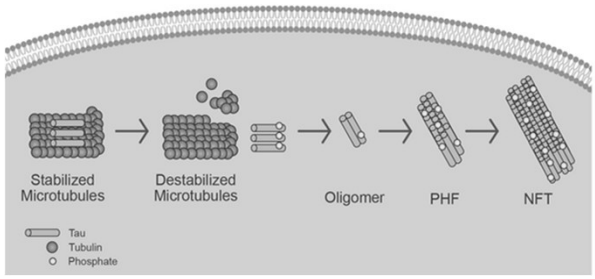


Alzheimer's Disease

- Progressive Neurodegenerative condition
- Amyloid and Tau accumulation along with degeneration of neurons
  - Amyloid Beta species – transmembrane protein abnormally cleaves
    - AB40 and AB42 most toxic and prevalent
  - Phosphorylated Tau – more specific to AD
- Neurodegeneration – Death of brain cells from progressive accumulation of abnormal proteins/destabilization of neurons

Image source: nia.nih.gov

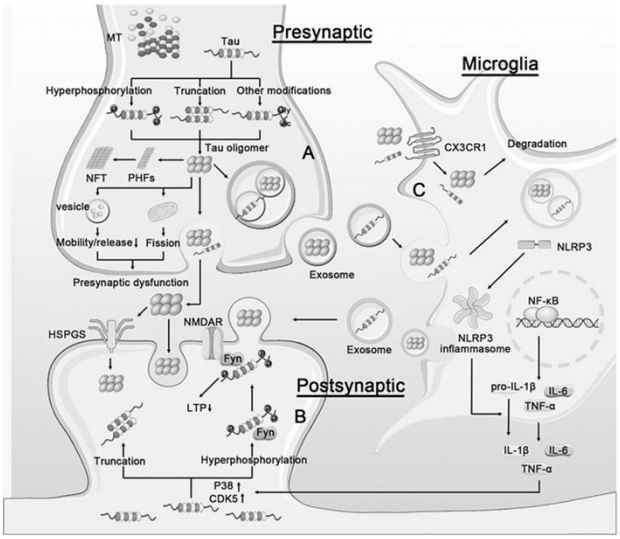
Alzheimer's Disease



- Initial – Preclinical (years)
  - Accumulation of amyloid without significant accumulation of tau
  - No clinical symptoms (or non neurologic symptoms)
- Clinical stages
  - Significant amyloid deposition and disruption of synapses
  - P-tau propagation and accumulation (prion-like)
  - Tau involved in cell transport/microtubule formation
  - Abnormal microglial activation
  - All of the above leading to neurodegeneration

Alzheimer's Disease

- Other factors
  - Inflammatory cytokines
  - Cell transport impairment
  - Synaptic compromise
  - Break down of blood brain barrier
  - Vascular changes



Jalili, C., et al.: Brain targeting based nanocarriers loaded with resveratrol in Alzheimer's disease: a review. IET Nanobiotechnol. 17(3), 154–170 (2023). https://doi.org/10.1049/nbt2.12127

Alzheimer's Disease Facts

- Risk Factors
  - Age > 65 (greatest)
  - Diabetes, Htn, HLD
  - Midlife Htn and Midlife Obesity
  - Family History
- Clinical Symptoms
  - Progressive cognitive and functional decline
  - Memory loss, sense of direction loss, word finding difficulties
  - Reduced insight into condition

Diagnosis

- Cognitive signs
  - Short term memory loss (Amnestic memory loss)*
  - Visuospatial dysfunction
  - Naming difficulties (lexicon selection)
  - Executive dysfunction
- Imaging
  - MRI – Atrophy of Hippocampi, parietal lobes
    - Hippocampal atrophy + Amnestic memory loss
- Blood Work Rule Out
  - Normal TSH and B vitamin testing
  - CBC/Chem panel within normal limits

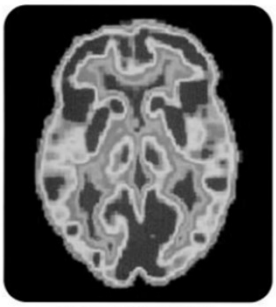
Diagnosis

- Biomarkers
  - CSF Amyloid and Tau
    - Mayo Clinic and Athena
    - Amyloid Beta 42, p-tau 181, Total tau and p-tau/AB
    - Usually at least 3 of 4 positive with reasonable clinical history is diagnostic
    - p-tau ratio correlates highly with Amyloid PET positivity
  - Blood based biomarkers
    - Amyloid Beta 42 and 40
    - p tau 181 and p tau 217

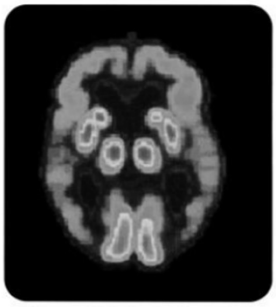
Biomarkers

- Limitations
  - CSF
    - Procedure
    - Still need to associate clinical symptoms with positive results
    - Interpretation if not clearly positive
  - Blood based
    - Not studied in wide range gen pop
    - Family hx
    - Not covered by insurance

Imaging



PET Scan of Normal Brain



PET Scan of Alzheimer's Disease Brain

- FDG PET scan
  - Hypometabolism patterns
    - AD is temporoparietal hypometabolism
    - Variants with different patterns
- Amyloid PET scan
  - Pittsburgh compound (PiB)
  - Amyvid (Florbetapir)
  - Tags Amyloid directly, much more specific
- Tau PET
  - Research exclusively

Treatments

- Initial
  - Cholinesterase inhibitors
    - Mild to moderate dementia
    - Modest benefit only, but consistent results in studies
    - Donepezil, Rivastigmine, Galantamine
  - Memantine
    - NMDA receptor antagonist
    - Moderate to severe dementia
    - Modest benefit only, but consistent results in studies

New Treatments

- Anti Amyloid therapies
  - Monoclonal antibodies to different toxic amyloid species
  - Infusion therapies (every 2 or 4 weeks)
  - 18 month duration
  - Mild cases only
  - Requires comprehensive oversight and management

New Treatments

- Eligibility
  - CSF confirmed Alzheimer's Disease
  - Mild Cognitive Impairment or Mild Dementia
  - Age < 85
  - No significant amyloid angiopathy on MRI
  - No anticoagulation
  - Able to get multiple MRI scans
  - APOE status
    - E4/E4 significantly increases risk of ARIA, but NOT exclusionary

Lecanemab

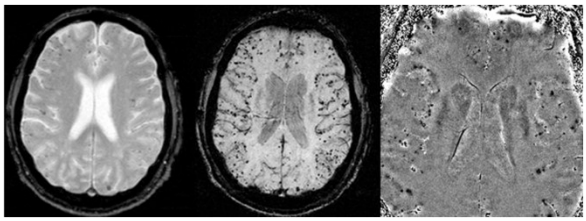
- Mechanism of action
  - Monoclonal Antibody targeting soluble amyloid
- Results
  - 25-30% slowing of progression
    - CDR-SB score
  - Significant reductions of abnormal amyloid
- Side Effects
  - ARIA (E or H) of ~ 20%
  - Infusion reaction ~25%

Donanemab

- Mechanism of action
  - Monoclonal Antibody
  - Targeting Amyloid plaques
- Results
  - Significant reduction of amyloid
  - Slowing down of progression ~35% based on iADRS
  - Better with low tau burden
- Side Effects
  - ARIA (E or H) of approximately 35%

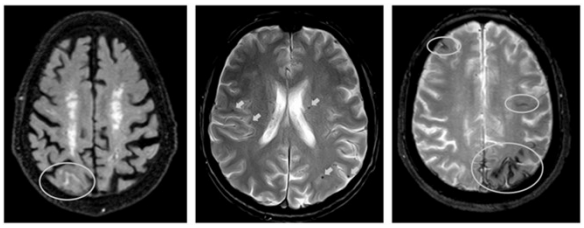
ARIA

- Amyloid Related Imaging Abnormalities
  - ARIA-H
    - Microhemorrhages or superficial siderosis
    - Permanent
    - Halt therapy until subsequent MRI shows stability
    - Macrohemorrhage is very rare



ARIA

- Amyloid Related Imaging Abnormalities
  - ARIA-E (Edema)
  - Swelling from abnormal immune response
  - Resolves without treatment usually
  - Halt until MRI shows resolution



Future Treatments

- Small Molecule
- Anti Tau
- Drug repurposing (ie, Atomoxetine)
- Neural stimulation (TMS, light and sound wave therapy, etc).
- Gene Therapy
- Lifestyle interventions for pre clinical

Cognitive Clinical Practice

- Clinical Diagnosis
  - Cognitive evaluation, imaging/blood work, Neuropsychologic testing
- Treatment with Cholinesterase Inhibitors
- Discussion of other options (Trials or infusions) in detail
- Spinal Tap for confirmation
- Review of results and further discussion
- Initiation of anti amyloid treatments