PATHOPHYSIOLOGY OF ALZHEIMER’S DISEASE
DIRECTION OF RESEARCH AND EMERGING TRENDS

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Scope of Alzheimer’s Disease

- 5.3 million people effected in US (2009)
- $300 billion cost to economy
- $60k per person per year
- 65.7 million cases worldwide (2030)
- 115.4 million cases worldwide (2050) (14 million US cases)
- $1 trillion cost to US economy (2050)
Projected Alzheimer’s Disease Prevalence 2000–2100

Projected Alzheimer’s Disease Prevalence,* 2000–2100

*PhRMA projections calculated by applying current prevalence rates to population projections.

Data sources: U.S. Census Bureau²; Hebert et al.³
Prevalence of Alzheimer's Disease with Age

*Values range from 30% to 47%, depending on source of data*
Figure 4.2
Yearly Cost per Patient of Selected Medical Conditions:
United States US$/Patient/Year

- Alzheimer
- Schizophrenia
- Cancer
- Stroke
- Coronary Heart Disease
- Diabetes
- Congestive Heart Failure
- Depression
- Osteoporosis
- Arthritis
- Hypertension
- Asthma

Source: WHO, 2020
Estimated Number of New AD Cases, in Thousands

US Contribution to Medical Research

- $15.6 billion Cancer
- $1 billion Cardiovascular
- $500 million Alzheimer’s Disease
Currently Approved Treatments

- Cholinergic and Antiglutamatergic treatment
- Offer some symptomatic relief of pain and suffering of patients and families
- No effect on natural disease course
- No effect on eventual outcome of disease
- If disease modifier were available that could delay onset by 1yr would have 9.2 million fewer cases by 2050
Dementia – Definition

- An unusual loss of mental function
- Acquired, persistent impairment in multiple areas of intellectual function not due to delirium
- A symptom of many diseases, not a diagnosis
Differential Diagnosis of Dementia

Vascular dementias
- Binswanger’s disease
- Multi-infarct dementia
  - Vascular dementias and AD

Dementia with Lewy bodies
- Parkinson’s disease
- Diffuse Lewy body disease
- Lewy body variant of AD
  - AD and dementia with Lewy bodies

Other dementias
- Frontal lobe dementia
- Creutzfeldt-Jakob disease
- Corticobasal degeneration
- Progressive supranuclear palsy
- Many others

AD

Causes of Alzheimer’s Disease

Tangles and Plaques

- Clinical and pathological description, Alois Alzheimer, 1906

- “Plaques and tangles” remain hallmarks for disease (Jellinger & Bancher 1998)
Alzheimer’s Disease – 2 types

- Familial - under age 60; mutations of genes 1, 14, 21; accounts for <10%

- Sporadic - late life onset; accounts for 90%
AD: Racial and Ethnic Influences

- Higher prevalence among blacks and Latinos than whites
- Greater familial risk in blacks
- Blacks and Latinos live longer with AD
- Genetic and environmental factors may work differently to cause AD in different races/ethnic groups
Advanced age

Female gender (1.5x)

Family history - 80% of cases
  - Genetic factors: Down’s syndrome, Presenilin mutations and abnormal amyloid precursor protein gene, Apo E 4 allele

Head traumas, especially in preceding 10 yrs

Cerebrovascular/ cardiovascular disease

Cholesterol/ HDLs

Small head size & brain volume
Smoking – increases risk except seems protective for those with Apoe E4
Alcohol or drug abuse
Environmental toxin – aluminum, zinc, mercury
Industrial solvents and pesticides
AD – Risk Factors with Less Supportive Evidence (cont’d)

- Infectious processes
- Low educational/occupational attainment
- Thyroid disease
- Being single during middle-age
A.D. – Theories of Causes

- Genetic
- Amyloid
- Tau
- Cholinergic/ neurotransmitter
- Recurrent systemic infections/ inflammation
- Head Trauma
- Old theories - aluminum/ toxins, autoimmune
Alzheimer’s Progression

- Synaptic instability, neuronal loss, and neurotransmitter dysfunction
- Targets crucial memory structures entorhinal cortex, hippocampus, association cortexes and cerebral default network leading to regional to diffuse damage
- Acetylcholine deficits predominate
AD Progression through Brain
Genetic Theories

Genes alone don’t cause AD

- 4 genes account for ~30% of AD; 50% of AD genetics are undetermined (Tanzi, 10)
- APP, PS1 & PS2 - early onset
- APOE 4 - late onset, increased risk in 70s
  - 20% of people are carriers of this type of APOE
  - If one copy, increased risk 3x
  - If 2 copies, 10x increased risk
Ataxin1 gene mutation – regulates how much \( \text{A} \beta \) is made

ADAM10 - regulates alpha-secretase cleavage of APP and increases \( \text{A} \beta 42 \)

SORL1 – allows APP to be converted into toxic form, cross cultural study, N = 6000 (2007); conflicting recent studies (2008)

CALHM1 – increased risk of AD by 45%, 2 copies of gene increased risk by 77%
  - Seems to interrupt ability of brain to take in calcium (critical for memory)
  - Also influences beta amyloid (2008)

Maternal link seems strongest
A.D. – Pathology Overview

- Atrophy & neuronal loss in n, hippocampus (elevation in floor of lateral ventricles, major role in memory) & related structures
- Neuritic plaques – amyloid
- Amyloid deposits in cerebral cortex, hippocampus & meninges
- Neurofibrillary tangles
- Role of inflammatory processes
Alzheimer’s Brain

Normal Brain
Healthy Brain vs. Advanced Alzheimer’s
Central Nervous System

- Consists of neurons and glial cells (microglia and astrocytes)
- Electrical transmission inside of nerves
- Chemical transmission between nerves
  - Neurotransmitters
    - Acetylcholine – for learning and memory
    - Glutamate – for fast excitatory synapses
Healthy Nerve Cells
Healthy Brain Physiology
Alzheimer’s Cells and Healthy Cells
Pathologic changes

- Amyloid plaques
- Intra-neuronal tau neurofibrillatory tangles
Beta Amyloid Plaque
Tangles

Tangles are forming

Healthy area

Tangles inside dying nerve cell
Neurofibrillary Tangles
Amyloid Cascade Hypothesis

- Increased production and or decreased clearance of Beta Amyloid protein
- Amyloid plaques formed as a result of abeta clearance from APP
- Sequence of steps involved in cleavage
Amyloid Precursor Protein

- Trans-membranous protein
- Essential component in brain processes
- Coded for on Chromosome 21
Protease Enzymes

- Alpha Secretase
- Beta-secretase
- Gamma Secretase
Beta-Amyloid Plaque
Most genetic mutations increase $A\beta_{42} : A\beta_{40}$ ratio

Normal ratio is 10 : 90

$A\beta_{40}$ is not as bad as $A\beta_{42}$

42 vs. 40 is dependent on where the clipping occurs
Snips of A Beta 42 – Oligomers

Monomer - one piece

Two stuck together – dimer

Three together – trimer

Four together – tetramer

Six together – hexamer

A $\beta$ 42 hexamers stacked up are most toxic and form plaques
Cu & Zn drive this reaction

Monomer

Oligomer

Proto fibril

β amyloid fibril

Non-pathogenic

Synaptic dysfunction
Dendritic pruning

Membrane disruption

Gliosis and inflammation
Amyloid Cascade limitations

- Amyloid plaques found in 30% of normals in their 70’s
- Role of NFT’s who’s cellular burden correlates more closely with disease activity
Link between Structural Changes and Cognitive Function

- Structural changes are also present in brains of non-demented older adults (Snowden’s Nun study)
- 1 in 3 non-demented 85 year olds have enough amyloid deposits in cortex to meet criteria for diagnosis of A.D.
Neurons have an internal support structure partly made up of microtubules. A protein called *tau* helps stabilize microtubules. In AD, *tau* changes, causing microtubules to collapse, and *tau* proteins clump together to form neurofibrillary tangles.
Amyloid deposits interfere with nerve cell communication at synapses

- Degree of AD dementia correlates with synaptic loss (Tanzi)
Stage 1: soluble oligomers of abeta lead to neurotoxicity, then to fibril formation and eventually plaques.

Stage 2: NFT’s deposited leads to neuronal and synaptic injury with ensuing neurotransmitter dysfunction. This stage thought to progress independent to amyloid burden.
Other Pathologic Processes

- Mitochondrial dysfunction
- Neurovascular dysfunction
- Insulin resistance and hyperinsulinemia
- Oxidative stress
- Abnormalities of trace elements
Copper/ Zinc Hypothesis of AD

Aβ + Cu/ Zn

- Oligomerization
- Fibrillization

Impairment of signal transmission

Beta amyloid plaques
- A β 42 exhibited antimicrobial activity against 8 organisms
- Activity correlates with oligomerization – A β 42 more potent AMP than A β 40
- AD temporal lobe had significantly greater antimicrobial activity than control temporal lobe
  - Anti-A β attenuated microbial activity
Brain Innate Immune System
(Tanzi, 10)

- Triggered by
  - Inflammation
  - Stroke
  - Traumatic brain injury
  - Chronic, sub-acute, or transient infection of CNS

- All increase Aβ levels
How Alzheimer's Disease Works (Tanzi)

- Insults to brain: CVA, TBI, neurotoxins, infection
- Innate immune response
- B secretase AB generation
- Genetic factors
- Neurotoxicity due to excessive levels of AB, Oligomers, inflammation
- Accumulation of brain AB, Aggregation vs. clearance, Synaptic injury
Progress in Clinical Research

- 1980-2000 primary focus on correction of neurotransmitter deficits
- 2000-present
  - Neurotrophic compounds
  - Amyloid directed therapies
  - Immunotherapy
  - Tau directed therapies
Inhibiting abeta production

- Gamma secretase modulators and inhibitors
- Inhibitors problems with Notch receptor protein
- Modulators
- Beta secretase inhibitors (problems with alternate substrates and blood brain passage)
- Alpha secretase stimulation
Anti-aggregants

- Tramiprosate (Alzhemed)
- Colostrinin
- Clioquinol
- Scyllo-Inositol
Vitamin B12, C, D, Folate no value unless deficiency

- Antioxidants, vitamin E, C beta-carotene
- Coenzyme Q10
- Resveratrol, coconut oil, curcumin, green tea
- Ginkgo biloba
Amyloid Removal

- Abeta degrading enzymes
- Immunotherapy
Active Vaccine

- Target vaccine towards Abeta
- AN1792,QS-21
- Adverse effects: vasogenic edema and meningoencephalitis
- Some clinical positive effects
- Clearance of plaques on autopsy
Passive Vaccination

- Monoclonal antibody targeted at various abeta fragments
- Bapeneuzamab and Soleneuzamab trials completed
- Bapeneuzamab no effect on clinical endpoints
- Soleneuzamab some effects on early patients but study not powered to assess efficacy vs placebo
Second Generation Active Vaccines

- CAD106, PF1010
- Staggered immunization protocol
- Less vigorous T-Cell response
- Targeted B-Cell response
Tau Directed Therapies

- MTC (methylthionimium Chloride) Rember
- Lithium
- GSK3B targets
- May have role in treatment of patients with clinical dementia
MCI Directed Research

- Active Vaccination with Second Generation agents
- New role for passive immunotherapy
- Potential role for secretase inhibitors
Alzheimer’s Disease Progression

**AD Progression**

- **Abnormal**
- **Normal**
- **Time**

- **Presymptomatic**
- **eMCI**
- **LMCI**
- **Dementia**

- FDG-PET
- MRI hippocampal volume
- CSF Aβ42
- Amyloid imaging
- Function (ADL)
- CSF Tau

Identification Based on Cognitive Testing
Biomarker Identification

![Graph showing progression to AD for Normal CSF and Pathological CSF](image)

**Numbers at risk**

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Amyloid Imaging Identification

[Images of brain scans showing different conditions]

- AD
- HC
- MCI converter
- PIB
- MCI non-converter
Onset of Alzheimer’s Disease Path

- **Presymptomatic AD**: No symptoms, biomarker evidence of amyloid dysregulation
- **Modified Dubois criteria: “earlier AD”**: Very mild symptoms + amyloid biomarker
- **Dubois research criteria: “early AD”**: Episodic memory impairment + any biomarker
- **Standard diagnosis**: Dementia

While plaques and tangles remain the structural markers of disease they may not play an actual role in disease progression.

Amyloid pathologic changes are likely occurring decades prior to clinical onset of disease.

Altering amyloid activity in clinical disease has limited if any value.
Future of Alzheimer’s Research

- Focus on early detection through improved clinical and biomarker analysis
- Early Disruption of amyloid cascade in first stage of progression
- Hope still exists for altering disease of those already effected through Tau mediated and neuroregenerative mechanisms
- If left unaltered Alzheimer’s will become the single greatest health care expense in the near future