Alzheimer’s Disease
A Clinical Update

Jonathan H. Woodcock, M.D.
Assistant Professor of Neurology and Psychiatry
Clinical Director, Memory and Dementia Clinic and Alzheimer’s Disease Research

October 30, 2014

Grand Rounds
Division of Geriatric Medicine
University of Colorado – Anschutz Medical Campus
Support:
Dana Foundation
Objectives

At the conclusion of this presentation, the participant should be able to:

• State how failed clinical trials based upon the *Amyloid Hypothesis of AD* are influencing understanding of the etiology of AD and future clinical trials.

• Summarize the challenges and potential research and treatment opportunities presented by the *Prion Protein Hypothesis* of progression of degenerative neurologic disease.

• Utilize new information regarding *AD risk factors* in counseling patients and families.
Alois Alzheimer

- 1864 – 1915, German
- Case: 51 year old woman,
- progressive
  “presenile” dementia,
  prominent delusions
    - Seen: 1901
    - Presented: 1907
    - Published: 1911
- Neuritic plaques
- Neurofibrillary tangles
AD – Current Criteria (2011)  
National Institute on Aging  
Alzheimer's Association

• Three phases of AD are recognized:
  – an asymptomatic biomarker-positive phase
  – a phase with positive biomarkers and mild cognitive deficits
  – a dementia phase

• Alzheimer's disease (AD) can be identified prior to the occurrence of dementia by using biomarkers (CSF, plasma aβ, tau, p-tau, amyloid imaging, medial temporal / hippocampal, whole brain volume)
AD - Biomarkers

• Used to “link” AD-C and AD-P
• Formal part of pre-clinical phase criteria only
  – Considered temporally: first aβ accumulation, then neuronal injury
• Complimentary, optional in MCI / dementia phases
• Appropriate for research, clinical trials
• Require further standardization and validation
AD - Biomarkers

• Initiating /“Upstream”: aβ accumulation
  – CSF: decreased aβ 42
  – Amyloid PET

• Neuronal degeneration – Injury / “Downstream”
  – CSF: increased total tau, hyperphosphorylated tau
  – Decreased FDG PET (regional metabolism)
  – Volume loss: medial, basal, lateral temporal; medial, lateral parietal

• Cost: Athena, 3/13, CSF aβ, P-Tau, T-Tau, with ApoE: $1,831.75, after patient direct pay 15% discount

Jack, Brain 2009;132(Pt5):1355-65
Alzheimer’s Disease
Clinical Criteria

• Dementia defined by clinical criteria including cognitive screening
• Deficits in ≥ 2 areas of cognition, and progressive worsening of memory, and other areas, i.e. language, perception and motor skills (praxis)
• Absence of disturbed consciousness
• Exclusion of other brain diseases.

• Diagnosis correct 85% based on these criteria
Alzheimer’s Disease - Course

- “Pre-diagnosis” phase: Stepwise slow decline in memory and attention span (7+ years)
- Symptomatic phase: 5+ years
- Focal neurologic signs: think another process of co-existent process
DSM-5
Mild Neurocognitive Disorder
Diagnostic Criteria

• Evidence for *modest* cognitive decline in > 1 cognitive domains

• Based upon:
  – Patient, informant, clinician
  – *Modest* cognitive impairment: Neuropsych testing or other quantified measure

• Does not interfere with independence in ADL’s, but with more effort, compensation, accommodation needed

• Not only due to delirium

• Not better explained by another mental disorder

• Specify:
  – Diagnostic category
  – Behavioral disturbance: with / without
DSM-5
Neurocognitive Domains

- Complex attention
- Executive function
- Learning and Memory
- Language
- Perceptual motor
- Social cognition
Mild Cognitive Impairment
Risk of Progression to Dementia
Based upon Recognition Memory

• Cohort: 200 elderly
• Progression to dementia:
  – Total: 37%
  – Lower recognition memory scores: 52%
  – High recognition memory scores: 22%

Gomez-Torosa, Am J Ger Psych, 2012
Mild Cognitive Impairment
Amyloid PET

- 11-C-PIB PET

- N = 31, amnestic MCI

- Increased PIB N = 17 (55%, especially ACC, PCC)
  - 14/17 converted to AD (82%) in 3 year f/u (47% in 1 year)

- Quicker conversion with higher amyloid load and with ApoE e4 allele

Neurology (2009) July 22 (e pub)
DSM-5
Major Neurocognitive Disorder
Diagnostic Criteria

• Evidence for *significant* cognitive decline in > 1 cognitive domains
• Based upon:
  – Patient, informant, clinician
  – *Substantial* cognitive impairment: Neuropsych testing or other quantified measure
• Interference with independence in ADL’s, assistance needed at least with complex instrumental ADL’s
• Not only due to delirium
• Not better explained by another mental disorder
• Specify:
  – Diagnostic category
  – Behavioral disturbance: with / without
  – Severity: Mild: difficulties with instrumental ADL’s
    Moderate: difficulties with basic ADL’s
    Severe: fully dependent
Alzheimer’s Disease Variants

• Posterior cortical atrophy
• Logopenic primary progressive aphasia
• Korsakoff’s amnestic
• Emotional / behavioral onset
Alzheimer’s Disease Variants
Posterior Cortical Atrophy

• “aperceptive visual disturbances”
  – Fragments of Bálint’s syndrome, Gerstmann syndrome
  – Difficulty seeing / recognizing objects
  – Alexia with agraphia
  – Acalculia

• Initial: vague visual disorientation
• Relative preservation of memory
• Pathology: usually typical AD, but posterior
Alzheimer’s Disease Variants
Posterior Cortical Atrophy

– Failure in orientation of body schema with surrounding space
– Prosopagnosia
– Getting lost
– Loss of ability to read a map
– Right / left disorientation
– Park a car
– Set a table
– Dress
– Rare:
  • Visual field neglect
  • Bálint’s syndrome
  • Gerstmann syndrome
Alzheimer’s Disease Variants
Logopenic
Primary Progressive Aphasia

– Dysnomia: words, nouns
– Dysfluency, pauses, circumlocution
– Verbal fluency (generating lists of words)
– Word recognition, comprehension
– Repetition, reading, writing
Alzheimer’s Variants
Emotional / Behavioral Onset

• Emotional onset may precede memory / cognitive impairments
  – Paranoia, delusions
  – Agitation, anxiety
Alzheimer’s Variants
Korsakoff amnesic state at Onset

– Immediate memory intact
– Short, long term retentive memory lost
People with Alzheimer’s

• Alzheimer's Association, 2014
  – Now:
    – 5.2 million Americans
    – 200,000 younger than age 65
    – 700,000 deaths/year
    – Incidence may be slightly higher in women, but prevalence is 3 x higher due to longevity

• Mid century:
  – 13.8 million Americans
  – 1,000,000 new cases / year
Costs of Alzheimer’s

• Medicare payments for AD are
  – $214 billion / year
  – greater than 2.5 times other diagnoses

• 2013:
  15,000,000 family members and other unpaid caregivers provided 17.7 billion hours of care for dementia at a value of $220 billion

• Caregiver responsibilities:
  – women: men = 2.3 : 1
AD – Treatment Attempts

• +/- cholinergics: physostigmine, choline, lecithin

• Modest: Ach-esterase inhibitors
  – Some prolongation of independence, ? Behavior
  – Effect on memory less certain
  – Side effects: nausea, diarrhea, confusion, insomnia, nightmares

• Memantine: NMDA glutaminergic antagonist
  – +/- for behavior; negative for cognition
  – Approved for late stage
  – Side effects: hallucinations, agitation

• Amyloid vaccine: encephalitis in early trial

• Negative trials: cerebral dilators, stimulants, L-dopa, vitamins B, C, E, gingko biloba, estrogen, anti-inflammatories
Dementia – Screening Evaluation

- Montreal Cognitive Assessment (MoCA)
  - Mini Trails B
  - Copy cube (copy intersecting pentagons)
  - Clock drawing
- Mini Mental Status Evaluation (MMSE; Folstein, Folstein, McHugh)
  - Now under copy write protection
- Frontal Assessment Battery (FAB)
- Abstraction (similarities / proverbs)
- Judgment (social: found letter, found check)
- Problem solving
- Praxis
- Swallowing
- Falls / balance
- Vision – Hearing
- Psychiatric - Hallucinations
- Structural: MRI
- CBC, CMP, B12, RPR, TSH, (ESR, ANA, HIV, CRP, folate)
Alzheimer’s Disease Pathology

- amyloid plaques: central amyloid core with surrounding degenerating neurons (neuritic plaques)

- neurofibrillary tangles: hyperphosphorylated tau protein in double helical filament confirmation

- neuronal loss
Neurofibrillary Tangles (NFT’s)

- Hyperphosphorylated tau protein
  - Tubulin associated unit
  - Cytoskeletal protein
  - Promotes assembly of and stabilizes microtubules
  - Effects synaptic plasticity
  - Aggregates when hyperphosphorylated into NFT’s
Tau Protein
(tubulin associated unit)

• Component of microtubules
• Internal cell support structures
• Transport of nutrients, vesicles, mitochondria, chromosomes
• Stabilizes growing axons

• AD: tau is hyperphosphorylated
  - forming insoluble double helical fibrils
  - intracellular deposition: cell dysfunction, death

• Tau deposition in NFT’s correlates with onset of cognitive symptoms, dementia
Cognitive – Pathological Correlates

• Synaptic / neuronal loss >

• Neurofibrillary tangles >

• Amyloid plaques

• AD-P is present in 30% of cognitive normal elderly
  – (pathological, PET, CSF studies)

DeKosky, Ann Neurol 1990; 27:457-64
Terry, Ann Neurol 1991; 30:572-80
Savva, NEJM 2009; 360:2302-9
Ingelsson, Neurology 2004; 62:925-31
Amyloid precursor protein - APP
Sequential proteolysis

• 1<sup>st</sup> Step:
  – α secretase: non-amyloidogenic pathway
    (favored in non-brain cells)
  OR
  – β secretase (BACE; β site APP cleaving enzyme): amyloidogenic pathway
    favored in brain cells due to preponderence of BACE

Producing α or β CTF (C terminal fragments)

• 2<sup>nd</sup> Step: γ secretase: α or β CTF’s to produce
  40 or 42 aβ fragments
Amyloid Hypothesis of Alzheimer’s Disease

• Production of $a\beta$ fragments leads to cascade of events resulting in clinical AD

• Formation of oligomers (“toxic”) lead to the amyloid “cascade”
  - Local inflammation
  - Oxidation
  - Excitotoxicity (excess glutamine)
  - Tau hyperphosphorylation: formation of neurofibrillary tangles (NFT’s)
  - Synaptic plasticity
  - Cell death
  - Imbalance of neurotransmitters (ACh, serotonin, noradrenaline)

Symptoms of AD
Amyloid Hypothesis of Alzheimer’s Disease

- **42 aβ fragment**: most soluble, most likely to aggregate into fibrils (“non-toxic”), the major component of amyloid plaques

- **42 aβ / 40 aβ ratio** correlates with disease symptoms

- **40 aβ fragment**: major component of cerebral angiopathic amyloid
Aim of the Amyloid Hypothesis

• To provide a framework for research and clinical trials in AD

• Problems: absence of benefit from clinical trials has led to re-examination of the premises of the hypothesis and focus on still unknown pieces of the puzzle of AD pathology
Problems with Amyloid Hypothesis

• NFT’s and neuronal loss, not neuritic plaques, correlate with dementia

• Both NFT’s and plaques occur in nondemented aging, but less than in AD
Predictions of the Amyloid Hypothesis


- Other causes of AD would involve amyloid metabolism, production and clearance

- Other causes of AD risk reduction would involve amyloid metabolism, production and clearance

- \( a\beta \) is toxic

- Amyloid/\( a\beta \) should initiate neurofibrillary tangle dysfunction

- Reducing \( a\beta \) and plaques would ameliorate Alzheimer’s symptoms
Predictions of the Amyloid Hypothesis

• Other causes of AD would involve amyloid metabolism, production and clearance
  - Presenilin mutations (γ secretase effects) increase the deposition of amyloid and AD
  - apoE-e4 increases deposition of amyloid and risk of AD
  - increased copy load of APP increases AD risk (DS; duplication of APP gene)
Predictions of the Amyloid Hypothesis

• Other causes of *AD risk reduction* would involve amyloid metabolism, production and clearance

  - apoE-e2 decreases deposition of amyloid and risk of AD

  - Icelandic APP mutation affecting β secretase binding site: decreases AD risk and amyloid load

  - normal copy load of APP gene in DS deletion normalizes AD risk (? IDD risk)
Predictions of the Amyloid Hypothesis

$\alpha \beta$ is toxic

- Some evidence for some toxicity: synaptic effects

- Plaque formation can be a rapid and induce glial and neuritic changes

  BUT:

- Laboratory and animal model effects do not explain the massive cell loss seen in AD

- Substantial $\alpha \beta$ induced degeneration occurs only with additional microtubule associated tau (MAPT) mutations
Predictions of the Amyloid Hypothesis

- Amyloid/αβ should initiate neurofibrillary tangle dysfunction
  
  **BUT:**

  - The influence appears more in the other direction
    - αβ toxicity is dependent on tau expression
    - tau expression can modulate αβ toxicity
    - relationship between αβ and tau is uncertain
Predictions of the Amyloid Hypothesis

• Reducing aβ and plaques would ameliorate Alzheimer symptoms

  This appears to be true in animal models

  BUT:

  - Failure of multiple Amyloid Hypothesis based clinical trials

  - Plaque can be cleared from the brain without effect on NFT’s or cell death
Amyloid Hypothesis Based Clinical Trial Failures

- The first active vaccine clinical trial for AD, AN1792, was halted early in 2002 due to the development of meningoencephalitis in ~6% (18 of 300) of the enrolled moderate-to-severe AD patients
Amyloid Hypothesis Based Clinical Trial Failures

• Tramiprosate: \(a\beta\) aggregation inhibitor; no cognitive benefit; ? Impact on HPC atrophy

• Tarenflurabril: \(\gamma\)-secretase inhibitor: cleavage of APP into smaller oligomers, reduce \(a\beta42\); no effects

• Semagecestat: \(\gamma\)-secretase inhibitor: worse ADL’s and cognition; side effects: skin cancer, infections, blood effects
Amyloid Hypothesis Based Clinical Trial Failures

- Bapineuzumab: passive immunization with monoclonal ab to plaque. High incidence of micro-hemorrhages, modest effect on PIB, p-Tau.

- Solanezumab: ab to soluble aβ; failed primary endpoints, met some secondary endpoints

- IVIG (Gammagard): anti-aβ ab’s
Problems with Amyloid Hypothesis: Amyloid and Tau

- The physiologic and pathologic roles of amyloid remain largely unknown
- Any causal relationship between amyloid and tau / NFT’s remains unknown
- NFT’s and neuronal loss, not neuritic plaques, correlate with dementia
- Both NFT’s and plaques occur in nondemented aging, but less than in AD
The failure of multiple AH based Clinical Trials – Possible Explanations

- The horse is already out of the barn: therapy was too late
- It’s the wrong horse: the therapy targeted the wrong toxic aβ oligomer
- It’s not a horse: the cause is not amyloid, but tau or another substance or pathway
- It takes more than a horse: the “double-hit”

Amyloid is part of the problem, but a combination of amyloid + another pathology is required to initiate AD pathology (i.e. vascular, tau, inflammation, genetic alteration, pathology X)
Prions

Proteinaceous infectious particles
Prion Paradigm Hypothesis
“Seeded protein aggregation and spread”

• Specific proteins *misfold* and *aggregate* into *seeds* that structurally corrupt like proteins, causing them to aggregate and form pathogenic assemblies.

• The aggregated proteins gain a *toxic* function and / or *lose* their normal function.

• The aggregated proteins *spread* along functional anatomic circuits

Prion Paradigm Hypothesis
“Seeded protein aggregation and spread”

• Systemic march of pathogenic protein along neuronal pathways
• Vulnerability of brain regions correlates with the strength of the neuronal connections
Protein Aggregate Formation

- De novo
- Genetic
- Infectious

“Amyloid”

- Multimeric proteinaceous assemblies
- Distinctive histochemical features: reddish / green birefringence under cross-polarized light after staining with the dye Congo-red
- Cross-$\beta$ quaternary structure by X-ray fiber diffraction analysis
- Amyloid state proteins are highly thermodynamically stable.
- Protective cellular mechanisms mitigate against their formation and for their removal.

Assembly of β-Amyloid sheets

Prion Paradigm Hypothesis
“Seeded protein aggregation and spread”

• Long silent phase of pathogenesis preceding the onset of symptoms
• Small, soluble proteinaceous seeds may be valuable as:
  – disease markers
  – therapeutic targets.

Prion Paradigm Hypothesis

Therapeutic targets

• Reducing production of aggregates / seeds
• Increasing removal of aggregates / seeds
• Stabilize native conformation of the protein (i.e. transthyretin amyloidosis)
• Stabilize existing aggregates to hinder fragmentation and seeding
• Prevention of corruptive templating by the cross-\(\beta\) sheet
• Arresting seeds as they cross neuronal connections
• Regulating the cellular processes of release, reuptake and transport of aggregates / seeds

AD – Pathology Progression
Brack and Brack (1991)

– Transentorhinal cortex
  • Entorhinal cortex
  • Hippocampus (CA1, CA2)
  • Subiculum
  • Amygdala
  • Parahippocampal gyrus

– Limbic
  • Anterior nucleus of thalamus
  • Septal nuclei
  • Diagonal band of Broca
  • Nucleus basalis of Meynert (cholinergic substantia innominata)
  • Locus ceruleus (noradrenergic)
  • Brainstem monoaminergic systems

– Spreading neocortical involvement
  • Posterior temporal – parietal neocortex
  • Diffuse cerebral cortex
The Papez Circuit

A: amygdala
H: hippocampus
PHG: parahippocampal gyrus

MB: mammillary body
AN: anterior nucleus of thalamus
CG: cingulate gyrus
T: thalamus
Abnormal aggregation of proteins

• More than 30 different amyloidogenic proteins have been linked to disease
• oligomers, protofibrils: intermediate assemblies can be toxic

  – AD: Aβ42
  – FTD: tau, TDP-43, FUS (fused in sarcoma)
  – DLB: α synuclein
  – PD: α synuclein
  – HD: polyglutamine repeats
  – Prion / Creutzfeldt – Jakob: prions
  – SOD-1 (Superoxide dismutase-1): ALS
  – Tumor suppressor protein p-53 (aggregates ineffective: tumor growth)
a, e: amyloid plaque progression in Alzheimer’s disease
b, f: tau in NFT progression in Alzheimer’s disease
c, g: a-synuclein in Lewy body progression in PD, LBD
d, h: TDP-43 inclusion in ALS, CBD

Apolipoprotein E

apoE
ApoE

• Chromosome 19
• Regulator of lipid / cholesterol metabolism
• Related to amyloid processing and clearance
• Role in AD is complex and uncertain
• Susceptibility risk factor for AD
ApoE

- **e2 allele:**
  - best for amyloid clearance
  - decreased frequency in AD

- **e4 allele:**
  - 25 -30% of US population carrier single allele
  - 60% of AD
  - Increases low density lipoproteins
  - Associated with increased Aβ deposition and Plaque formation
  - Lowers age of onset of familial (early) and later onset AD (LOAD)
  - Homozygous e4 alleles lead to very high AD risk by the 80’s
  - Increased *RISK*, not deterministic
apoE

- ApoE alleles: e4 – e3 – e2
  - Graded association with:
    - Higher total cholesterol and triglycerides
    - Lower HDL cholesterol
    - Lower total ApoE levels
    - Higher amyloid plaque formation
  - Increased (e4) / decreased (e2) risk of Alzheimer’s disease (at earlier / later age)
APOE and Alzheimer disease: a major gene with semi-dominant inheritance

Cohort: 17,483 85-year-old Americans
7,351: Alzheimer's
10,132: No Alzheimer’s

<table>
<thead>
<tr>
<th>Risk</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>11%</td>
<td>14%</td>
</tr>
<tr>
<td>1 copy APOE-e4</td>
<td>23%</td>
<td>30%</td>
</tr>
<tr>
<td>2 copies APOE-e4</td>
<td>51%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Comparison: **BRCA1 gene**. Women with an abnormal BRCA1 gene have risk of developing breast cancer during their lifetimes of between 50 percent and 60 percent.

Genin, Molecular Psychiatry, 2011
Apolipoprotein E (APOE) Positive Predictive Value in Clinical AD

• Athena: In individuals who have a clinical diagnosis of Alzheimer's disease, the probability that AD is the correct diagnosis increases 97% in the presence of Apo E4/E4.
Very low levels of apoE may not be associated with any cognitive impairment

- 40-year-old African American man
- homozygous for a rare frame shift loss-of-function mutation in apoE
- severe dysbetalipoproteinemia and xanthomatosis
- undetectable levels of apoE in plasma and CSF
- cognitively normal and shows no signs of neurodegeneration

Mak, *JAMA Neurology* 2014
Brain Differences in Infants at Differential Genetic Risk for Late-Onset Alzheimer Disease - A Cross-sectional Imaging Study

ε4 carriers had:
- lower White matter myelin water fraction (MWF) and Gray matter volume (GMV) measurements than noncarriers in precuneus, posterior/middle cingulate, lateral temporal, and medial occipitotemporal regions, areas preferentially affected by AD
- greater MWF and GMV measurements in extensive frontal regions
- attenuated relationship between MWF and age in posterior white matter
Directions for Future Research

• It’s not a horse – It takes more than a horse

Alternative primary pathology / “double hit”
  – Tau, vascular, inflammation
  – Genetic models: DS, APP, PSEN, apoE (bexarotene)
    • Autosomal dominant AD (ADAD): The Dominantly Inherited Alzheimer Network (DIAN), a collaborative effort of international AD center
  – Co-factors, cytokines (Leukine / GM-CNS)
  – Glucose and lipid metabolism (insulin: SNIFF)
  – Prion protein model of anatomic circuit self propagation by permissive templating of aβ and tau
  – Sleep associated clearance of amyloid
Mouse models with familial Alzheimer’s disease (FAD) mutations exhibit amyloid-$\beta$-induced synaptic deficits memory deficits
BUT NOT
other key pathological events of Alzheimer’s disease, including distinct neurofibrillary tangle pathology.

(Recently developed rat AD model does develop NFT)

Human neurons derived from Alzheimer’s disease patients have shown:
elevated levels of toxic amyloid-$\beta$ species phosphorylated tau
BUT NOT
amyloid-$\beta$ plaques neurofibrillary tangles
A three-dimensional human neural cell culture model of Alzheimer’s disease

Se Hoon Choi¹,²*, Young Hye Kim¹,²*, Matthias Hebisch¹,³, Christopher Sliwinski¹, Seungkyu Lee⁴, Carla D’Avanzo¹, Hechao Chen¹, Basavaraj Hooli¹, Caroline Asselin¹, Julien Muffat⁵, Justin B. Klee¹, Can Zhang¹, Brian J. Wainger⁴, Michael Peltz¹, Dora M. Kovacs¹, Clifford J. Woolf³, Steven L. Wagner⁶, Rudolph E. Tanzi¹ & Doo Yeon Kim¹

- Human neural stem-cell-derived three-dimensional (3D) culture system
- FAD mutations in
  - b-amyloid precursor protein and
  - presenilin 1
- robust extracellular deposition of amyloid-β,
- amyloid-β plaques,
- neuronal cells expressing FAD mutations exhibited
  - high levels of aggregates of phosphorylated tau in the soma and neurites
  - filamentous tau, as detected by immunoelectron microscopy.
Treatment Effects:

- Inhibition of amyloid β generation with β- or γ-secretase inhibitors
  - decreased amyloid-β pathology
  - attenuated tauopathy

- Glycogen synthase kinase 3 (GSK3) regulated amyloid-β-mediated tau phosphorylation.
Summary:

• This 3D neural cell culture model recapitulated Alzheimer’s disease pathology
• May allow for more efficient screening of potential drug treatment models
• May facilitate the development of more precise human neural cell models of other neurodegenerative disorders