Diagnostic Biomarkers and Treatment Options for Alzheimer's Disease.

Jeffrey M. Burns, MD
Edward H. Hashinger Professor of Neurology
Associate Director, KU Alzheimer’s Disease Center
Director, Clinical and Translational Science Unit
Dementia Criteria

1. Decline in cognition
   - Memory
   - Executive Function: Planning / Organization
   - Language
   - Orientation

2. Interferes with everyday function
Clinical Hallmarks of Dementia

- Gradual onset
- Progressive decline
- Memory loss
- Other cognitive domains impaired
- Interferes with function
Causes of Dementia

- Alzheimer’s Disease: 50 - 70%
- Dementia With Lewy Bodies: 15%
- Vascular Dementia: 10%
- Frontotemporal Dementia: 5%
- Other
Alzheimer’s Disease

• Most common cause of dementia (50 – 70%)
• Marked by early memory impairment, executive dysfunction

Alzheimer’s Facts

• 5.2 million Americans have AD in 2008
• One in eight (13 percent) over 65 have AD
• Every 71 seconds someone develops AD
• $148 billion in direct and indirect costs to Medicare, Medicaid, and businesses.
Alzheimer’s Disease is Increasing Dramatically

Occurrence of AD increases exponentially with age

The population is aging at an unprecedented rate
New Alzheimer’s Criteria
McKhann et al 2011

• Key criteria remain unchanged
  – Identify intra-individual decline in cognition and function as salient clinical features

• Biomarkers: Consider the use of AD biomarkers to enhance confidence in the clinical diagnosis.
Early Cognitive Changes in Alzheimer’s Disease

Memory Loss
- Forgetfulness (conversations; appointments; medicines; names)
- Repetition of questions, statements
- Misplacing items

Executive Dysfunction
- Managing household finances
- Driving
- Meal preparation
- Operating appliances
Diagnosing AD

- Detailed History
  - Characteristics and pattern of changes
  - Importance of informant / caregiver
- Physical Examination
- MRI or CT to r/o structural process
- Lab work: TSH, B12
- Usefulness of AD biomarkers emerging
  - Currently, no brain scan or blood test can replace the clinical evaluation
Nondemented (CDR 0)

Follow-up Time
0 3 years

Very Mild Dementia (CDR 0.5)

Follow-up Time
7 years 8 years 10 years 11 years

Mild Dementia (CDR 1)

Follow-up Time
11 years 12 years 14 years

Moderate Dementia (CDR 2)

Follow-up Time
15 years
AD Biomarkers: Detecting the Alzheimer’s Signature

- Reflect
  - Molecular pathology (Amyloid, tau) of AD
  - Consequences of disease (atrophy, low metabolism, disrupted neural networks)

- Possible uses:
  - *Diagnosis* in symptomatic persons
  - *Prognosis* (e.g., rate of change)
  - *Screening* in asymptomatic persons
83 years old with AD
- MMSE 24/30
- May need assistance or cues with more complex tasks
85 years old
-MMSE 2/30
-Having difficulty with making a snack, choosing clothes to wear, discussing current events
Hippocampal volumes decline early in the disease

19 year old male

86 year old female with AD
Candidate CSF biomarkers of AD


Slide courtesy of John Morris
New Age of Molecular Imaging: Amyloid Imaging

Detection of Amyloid Plaques

Amyloid Plaques

Amyloid Label

PET Scanner

Amyloid PET Scan
Detecting Amyloid

Brain Pathology

- β-Amyloid burden = 0.15%
  Low likelihood of Alzheimer disease

- β-Amyloid burden = 1.63%
  High likelihood of Alzheimer disease

- β-Amyloid burden = 7.92%
  High likelihood of Alzheimer disease

AV-45 / Florbetapir

- Participant age at death, 82 y
  Mean cortical SUVR = 0.87, PET score = 0

- Participant age at death, 78 y
  Mean cortical SUVR = 1.17, PET score = 2

- Participant age at death, 79 y
  Mean cortical SUVR = 1.68, PET score = 4

Clark, C. M. et al. JAMA 2011;305:275-283
The Inappropriate Plumber

• 51 yo plumber
  – Altered short term memory for 4 years
    • Forgets where he parked his car, forgets conversations, sends repetitive emails.
  – Inappropriate behavior
    • “Crosses lines”; disinhibited conversationalist
    • Inappropriate jokes
    • Disinterested, decline in hygiene
  – Divorced; fired from his job as a plumber and later as a plumbing dispatcher
The Inappropriate Plumber

- Exam: normal; talkative, jovial, repetitive
- FH: father with AD (onset in 70s)
- Cognitive performance
  - MMSE 20/30
  - Episodic memory impairment (LM=1, delayed LM=0)
  - Dysexecutive (Stroop interference 6, Fluency: 9)
- MRI report – minimal atrophy
- PET report – bitemporal hypometabolism, no evidence of parietal hypometabolism
- Differential Diagnosis?
Behavioral Variant Frontotemporal Dementia

• Clinical features
  – Common dementia in those <65 yrs
  – Disinhibition, apathy, compulsive, dysexecutive
  – Imaging: frontal or temporal atrophy, hypometabolism

• Pathology: NACC study of 95 autopsy cases
  – Tau+ (30%) or tau- (50%) inclusions
  – AD pathology: 20%

Mendez et al. Neurology 2013
MRI: Unremarkable

CSF: consistent with AD profile
Amyvid Scan
Interpretation: There is diffuse Amyvid accumulation involving the frontal lobes bilaterally as well as the temporal lobes, bilateral occipital lobes, and the bilateral parietal lobes.
Amyvid Scans

Negative (SUVR 0.9)

Positive (SUVR 1.84)
The Inappropriate Plumber

Take-home points

• Atypical AD not uncommon
  – Clinical misdiagnosis of bvFTD can occur in those with early onset and neuropsych features

• AD biomarkers can enhance diagnostic confidence
  – In this case, AD biomarkers altered medications and allowed inclusion into clinical trials.
Presymptomatic Detection?

Amyloid –
Cognitively normal

Amyloid +
Alzheimer dementia

Amyloid +
Cognitively normal

3 years later, Alzheimer dementia
Asymptomatic Amyloid: What does it mean?

• 30% of healthy adults have brain amyloid
  – Not a diagnosis of AD
  – Not all develop AD

• Risk factor for developing AD
  – Magnitude and timing of risk not yet defined
    • Likely plays out over 10+ years

• New era of AD prevention trials
  – Identify individuals at higher risk for AD
  – Window of opportunity
KU Alzheimer’s Prevention Program

• Launched in late 2012
  – 2 years of planning

• Provide cognitively normal older adults with
  – AD risk profile and general health screen
  – Prescription for better health

• Foundation for the first AD prevention trials
  – Exercise (APEX – Oct 2013)
  – Anti-amyloid strategies (A4 trial – January 2014)
Alzheimer’s Prevention with Exercise (APEX) Trial

- Screen 400 cognitively normal older adults
  - Sedentary, Age 65+
  - Amyloid imaging (Amyvid)
  - Identify 100 individuals with brain amyloid

- 52-week aerobic exercise program in Kansas City YMCAs
  - Aerobic exercise (n=67)
  - Non-aerobic stretching/toning (n=33).
Approved AD Therapies

• Two classes of approved medications
  – **Cholinesterase inhibitors** → increase acetylcholine levels
    • Donepezil
    • Galantamine
    • Rivastigmine
  – **NMDA antagonist**
    • Memantine
Effect of Medications on AD Course

- Initiate Medications
- Donepezil
- Galantamine
- Rivastigmine
- Namenda

Cholinesterase inhibitors
Medical Therapy for Neuropsychiatric Symptoms

**Standard AD Therapies**

- **Cholinesterase inhibitors**
  - 5 of 8 studies reported significant benefits.

- **Memantine**
  - 2 studies with conflicting results

**Psychiatric Medications**

- **Atypical Antipsychotics**
  - Modest efficacy
  - Low doses effective
  - Increased risk of stroke/TIA
    - Risperdal: 3.3% vs. 1.1%

- **Antidepressants**
  - Effective for depression
  - May benefit agitation

- **Mood stabilizers** – valproate, carbamazepam
  - No evidence of efficacy
The Amyloid Hypothesis

Amyloid plaques trigger the AD pathophysiologic cascade

Production

Enhance Clearance

Downstream effects

Cell Death
Cerebral Amyloid is Reduced with Bapineuzumab
Early Results of Amyloid Therapeutics

- **2005: AN-1792**: active Abeta vaccination (Phase 2)
  - 300 AD participants – halted due to meningoencephalitis
  - Fewer Abeta plaques in brain despite dementia progression
- **2008: Flurizan** (tarenflurbil): reduces amyloid levels
  - 1649 mild AD participants: no evidence of efficacy
- **2009: Alzhemed** (tramiprosate): inhibits Abeta formation and deposition
  - 1052 AD participants: no evidence of efficacy
- **2010: Semagacestat**: gamma secretase inhibitor
  - 2600 AD participants: halted early due to greater rates of progression in treated participants
- **2012: Bapineuzumab**: antibody for amyloid
  - No effect in those with ApoE4 genetic risk
Thinking Beyond Amyloid

- Amyloid (plaques)
- Tau (tangles)
- Vascular (low blood flow)
- Metabolism
  - Insulin resistance
  - Mitochondria
- Genetics
Hope for the Future

Treatment and Prevention

• Identify brain changes early or before the onset of symptoms

• Halt or reverse the disease process
  – Drugs – anti-amyloid therapies (?)
  – Lifestyle interventions
Nationally-Designated AD Centers 2010
Nationally-Designated AD Centers 2011