Early diagnosis, biomarkers and intervention in Alzheimer’s disease

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Director, Alzheimer Disease Research Center
University of Washington
AD: the only leading cause of death that is increasing

6 million people with AD in the US

The biomedical challenge of our time
Failure to keep levels of diagnosis straight!
Confusing AD and dementia

• There is both public and professional conflation of AD and dementia.
• Statistics you hear on prevalence of AD (5.8M Americans) means AD dementia.
• Mild cognitive impairment due to Alzheimer’s disease is not being counted here.
• CPT codes from ICD-9 and ICD-10 mean AD dementia.
For every case of AD dementia, there are two cases of preclinical Alzheimer’s disease.
Cognitive diagnosis
”What’s wrong with the mind”

Normal cognitive aging
Subjective impairment
  Mild cognitive impairment
    Mild dementia
    Moderate dementia
    Severe dementia
Causal diagnosis
”What’s wrong with the brain”

• Alzheimer’s disease
• Vascular brain injury
• Lewy body disease
• Frontotemporal degeneration
• Parkinson’s disease
• etc
Messaging for urgent action ....

AD: the only leading cause of death that is increasing

6 million people with AD in the US

Excessive narrative of loss!
Are we already making progress?

- Even though the total number of cases of dementia due to Alzheimer's is increasing,
- The rate of Alzheimer’s disease among aging people has actually **declined** in U.S., Europe, Japan
  - Correlates with more education
  - Probably also reflects better primary care, notably better control of hypertension

Twenty-seven-year time trends in dementia incidence in Europe and the United States

Wolters et al, Neurology 2020
Outline

1. Diagnosis of mild Alzheimer’s disease
2. Role of biomarkers in diagnosis of AD
3. Recent developments in anti-amyloid therapy of AD
What is cognitive aging?

Normal cognitive aging is change in memory, word retrieval, processing speed, problem-solving, and other aspects of cognition due to aging processes, as opposed to disease.

Slower cognition, functionally insignificant word finding trouble, inefficient memory retrieval, less intense concentration and attention

Pathologic cognitive aging reflects the additional effects of disease.
Mild cognitive impairment
An intermediate state between typical aging and dementia

• Complaint/concern about a change in cognition
• Objective impairment in cognitive domain(s)
• Preserved functional independence
  • (Or in practice, only mild dependence)
MCI: a state of risk for dementia

Risk of conversion to dementia is about 10%/yr
Asymptote is 70% conversion overall, over 5-10 yrs
Of these, about 2/3 of converters have Alzheimer’s dementia
And the remainder a non-AD dementia
What is Alzheimer’s Disease?

Neurofibrillary Tangles (tau)

Amyloid Plaques

B
Six stages of AD tau tangles

Stage I and II

Stage III and IV

Stage V and VI
<table>
<thead>
<tr>
<th>Tau/NFTs</th>
<th>Memory loss</th>
<th>Cognitive loss</th>
<th>Sensorimotor sparing</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Early deposition in medial temporal lobe including hippocampus</td>
<td>• Then association cortex – especially posterior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Primary cortex last, motor cortex spared</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The central tendency in AD is for early involvement of memory-related brain regions.

The normal cognitive presentation of AD is amnestic mild cognitive impairment.
<table>
<thead>
<tr>
<th></th>
<th>Pre-Symptomatic</th>
<th>MCI</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>15+ years?</td>
<td>Medial Temporal</td>
<td>Limbic</td>
<td>Cortical</td>
</tr>
<tr>
<td>5+ years</td>
<td>6-10 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hippocampal atrophy
Hippocampal volume measurement

*Charts and normative values are provided for reference purposes only. The FDA has not approved their use for diagnostic purposes.*
NeuroQuant®
Age-Related Atrophy Report

PATIENT INFORMATION
Patient ID: 041_5_1010
Patient Name: 041_5_1010
Sex: M
Accession Number: Referring Physician:
Exam Date: 2009/01/12 12:00:00 AM

MORPHOMETRY RESULTS

<table>
<thead>
<tr>
<th>Brain Structure</th>
<th>Volume (cm³)</th>
<th>% of IC (95% CI)</th>
<th>Normative Percentile*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampi</td>
<td>6.37</td>
<td>0.37 (0.42-0.58)</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Lateral Ventricles</td>
<td>71.18</td>
<td>4.10 (0.96-4.04)</td>
<td>95</td>
</tr>
<tr>
<td>Inferior Lateral Ventricle</td>
<td>7.20</td>
<td>0.41 (0.11-0.29)</td>
<td>&gt; 99</td>
</tr>
</tbody>
</table>

AGE-MATCHED REFERENCE CHARTS*

*LCharts and normative values are provided for reference purposes only. The FDA has not approved their use for diagnostic purposes.
Factors increasing risk of conversion of MCI to dementia

- Amnestic profile of impairment
- Encoding problems (i.e. cueing does not help)
- Hippocampal atrophy at time of diagnosis
- Deficits extending beyond memory encoding (multidomain aMCI)

Mcevoy and Brewer
Diagnosis of MCI: Key points

• Memory loss for recently encountered material is a usual leading complaint in Alzheimer’s disease

• Give a measurable test of recent memory
  • Not normal to be unable to recall registered words after a few minutes
  • Definitely abnormal to be unable to recognize words in a multiple choice format

• Montreal Cognitive assessment (MoCA)
  • Reasonably sensitive to MCI
  • Score < 26 is abnormal

• For those with MCI, and MRI to determine whether there is hippocampal atrophy can help with counseling on prognosis and deciding whether to refer
Gotcha

• The prognosis of MCI is sensitive to its definition
• If there is no complaint, e.g. mild impairment is *discovered* through screening, conversion is less robust and reversion often occurs
• Here one strategy is to consider an abnormal screening result to be a baseline, and to see if there is change over time (e.g. one year)
The value of neuropsychological testing

• Neuropsychological testing is recommended for suspected MCI
  • Especially if there is a high level of baseline function
  • Especially if there are potentially developmental factors

• Strengths of this approach are:
  • Quantification, with implication that it establishes a clear baseline for followup
  • Systematic evaluation of possibly subtle impairments in other domains
  • Methods for estimating premorbid functioning make this approach well suited to those with high or low intellectual baselines
Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)

• 1260 at risk Finnish seniors CAIDE > 6
• Interventions:
  • diet,
  • exercise,
  • cognitive training,
  • vascular risk monitoring
Disease-modifying medication?

Symptomatic medication

Dementia-Friendly Community

Leverage Retained Strengths

Compensation

Build Cognitive Reserve

Vascular health

Mental health/Social belonging/Purpose

Sleep/Nutrition/Exercise/Cognitive activity

Cognitive Age

Normal cognition
Subjective memory concerns

Mild cognitive impairment

Dementia

Memory and Brain Wellness Center

2020

1990
Outline

1. Diagnosis of mild Alzheimer’s disease
2. Role of biomarkers in diagnosis of AD
3. Recent developments in anti-amyloid therapy of AD
Importance of amyloid plaques and tau tangles

- Defining **hallmarks** of Alzheimer’s disease
- **Biomarkers (Measures)** of Alzheimer’s disease
- Pathological **drivers** of Alzheimer’s disease?
Biomarkers

Measureable characteristics that signify disease processes

- Imaging tests – MRI, PET
- Spinal fluid protein levels
**A | T | N** biomarkers

**A : AMYLOID**
- Low amyloid protein in Cerebrospinal Fluid
- Amyloid PET

**T : TAU**
- High phosphorylated tau in CSF
- Tau PET

**(N) : NEURODEGENERATION**
- Atrophy detected by MRI
- Low metabolism detected by FDG PET
- High total tau in CSF

Jack et al, 2018
Langbaum, J. B. et al. (2013) Ushering in the study and treatment of preclinical Alzheimer disease

Canonical Sequence of AD Biomarkers

- CSFAB_{42}
- Amyloid PET
- CSF tau
- MRI + FDGPET
- Cognitive impairment

Degree of Abnormality

Latent/Presymptomatic | aMCI | Dementia
--- | --- | ---
Normal | High risk | Low risk
MCI | | 
Dementia | | 

Jack et al, 2013
Amyloid PET scans

NEGATIVE – NOT ALZHEIMER’S

POSITIVE – ALZHEIMER’S PLAQUES
• AT(N) radically respects the difference between syndrome and disease
• AT(N) defines specific biological states, targetable by interventions
• AT(N) operationalizes preclinical AD
Conversion of aMCI to dementia

Mcevoy and Brewer
Plasma amyloid biomarkers
Schindler et al 2019
Appropriate clinical use of A |T |N biomarkers?

• Atypical dementia
  • Young onset
  • Nonamnestic profile
  • AD vs FTD

• Confounding neurological processes
  • Dementia in multiple sclerosis
  • Older age epilepsy and cognitive impairment

• Persistent unexplained MCI

• In other words, in a specialty clinic
• But what if there is a treatment implication?
Primary Age-related tauopathy (PART)

Limbic-predominant Age-related TDP-43 disease (LATE)

- Degenerative hippocampal sclerosis
- TDP-43 proteinopathy
- A cause of amyloid-negative amnestic MCI and amnestic dementia
- Incidence ~ 50% by age 85

Crarry et al
Outline

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• Defining **hallmarks** of Alzheimer’s disease
• **Biomarkers** (Measures) of Alzheimer’s disease
• Pathological **drivers** of Alzheimer’s disease?
Amyloid cascade hypothesis

- Deposition of amyloid beta initiates Alzheimer pathophysiology.
- Amyloid beta exerts a toxic effect on its neuronal environment, possibly as soluble oligomers.
- Neuritic transformation of plaques and intracellular neurofibrillary pathology are secondary to amyloid effects.
Canonical Sequence of AD Biomarkers

Jack et al, 2013
Amyloid cascade, elaborated

- Rising Abeta42 Level
- Abeta42 Oligomerization
- Synaptic dysfunction
- Hyper-excitability
- Altered ion homeostasis & oxidative stress
- Tau Phosph’n
- Transsynaptic spread
- Inflammation
- Cortical neuron loss
- Energy failure, Aerobic glycolysis
- Microglial activation
- Vascular dysfunction
- Altered cellular signaling
Anti-amyloid monoclonal antibodies “mabs”

- Bapineuzumab - Pfizer
- Solanezumab – Lilly
- Gantenerumab – Hoffman-La Roche
- Aducanamab - Biogen
- Donanemab – Lilly/Eisai
Emerge and Engage Phase 3 Studies

- 50-85 y/o
- MCI due to AD (most), mild AD (small percentage)
- CDR 0.5, MMSE 24-30
- MRI without > 4 microhemorrhages
  - > 1 lacune
  - > grade 3 white matter hyperintensities

i.e. very mild AD, with minimal vascular component
Amyloid Mabs really do clear amyloid!

Sevigny et al
Clinical Endpoints *not* met, esp. in ENGAGE
Adverse Events: ARIA amyloid-related imaging abnormalities

Table 3: Adverse Reactions Reported in at Least 2% of Patients Treated with ADUHELM 10 mg/kg and at Least 2% Higher Than Placebo in Studies 1 and 2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADUHELM 10 mg/kg N=1105</th>
<th>Placebo N=1087</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIA-E</td>
<td>35%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache†</td>
<td>21%</td>
<td>16%</td>
</tr>
<tr>
<td>ARIA-H microhemorrhage</td>
<td>19%</td>
<td>7%</td>
</tr>
<tr>
<td>ARIA-H superficial siderosis</td>
<td>15%</td>
<td>2%</td>
</tr>
<tr>
<td>Fall</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>Diarrhea†</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Confusion/Delirium/Altered Mental Status/Disorientation†</td>
<td>8%</td>
<td>4%</td>
</tr>
</tbody>
</table>
FDA decision

- Accelerated approval based on biomarker evidence indicating a likely effect
- Post approval Phase IV randomized trial required
- But ... the CMS preliminary national coverage determination is now restricts coverage to a context of Clinical Evidence Development, i.e. a clinical trial
The controversy in a nutshell

- Aducanamab removes amyloid protein from the brain
- No clear-cut efficacy on cognition
- Politicization of the approval processes
- Mistakes were made
- CMS decision effectively severely restricts availability
Why do I bring this to your attention?

• As a class, anti-amyloid antibodies are likely to gain a role as more evidence develops
  • Converging evidence across trials
  • Evidence of favorable effect on “downstream” tau biomarkers

• These will target early disease, underscoring the value of making a diagnosis at MCI stage or earlier, which is our focus today

• Demonstrates the value of biomarkers in diagnosis and tracking disease
Donanemab (Lilly)

- Phase 2 (TRAILBLAZER) met primary endpoint on slowing decline
- Now moves in Phase 3
- Like aducanamab, significantly reduces amyloid burden
- Similar safety risk profile, rates of ARIA
- Also appears to slow the rate of NFT accumulation (by tau-PET scans)
Aducanumab significantly lowers plasma p-tau

**EMERGE**

- **Baseline Mean** (pg/ml): 3.19
- **Placebo**: 3.27
- **Low**: 3.35

**ENGAGE**

- **Baseline Mean** (pg/ml): 3.18
- **Placebo**: 3.24
- **Low**: 3.11

**Analysis visit (weeks)**

- **Baseline**: 0
- **56 weeks**: 13% decrease from baseline
- **78 weeks**: 8% increase from baseline

**Analysis visit (weeks)**

- **Baseline**: 0
- **56 weeks**: 9% increase from baseline
- **78 weeks**: 16% decrease from baseline

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Low dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>287</td>
<td>293</td>
<td>290</td>
</tr>
<tr>
<td>177</td>
<td>172</td>
<td>168</td>
</tr>
<tr>
<td>273</td>
<td>269</td>
<td>271</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Low dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>333</td>
<td>331</td>
<td>281</td>
</tr>
<tr>
<td>301</td>
<td>299</td>
<td>242</td>
</tr>
<tr>
<td>325</td>
<td>322</td>
<td>274</td>
</tr>
</tbody>
</table>
Greater reduction in plasma p-tau\textsuperscript{181} is associated with less clinical decline across all four clinical measures in both studies.

<table>
<thead>
<tr>
<th>Association between change in p-tau and efficacy at Week 78</th>
<th>Expected correlation</th>
<th>Correlation (p-value)</th>
<th>EMERGE (n=514–521)</th>
<th>ENGAGE (n=577–581)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-tau\textsuperscript{181}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDR-SB</td>
<td>Positive</td>
<td>0.11 (0.0166)</td>
<td>0.14 (0.0005)</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>Negative</td>
<td>-0.21 (&lt;0.0001)</td>
<td>-0.15 (0.0002)</td>
<td></td>
</tr>
<tr>
<td>ADAS-Cog13</td>
<td>Positive</td>
<td>0.17 (0.0001)</td>
<td>0.15 (0.0002)</td>
<td></td>
</tr>
<tr>
<td>ADCS-ADL-MCI</td>
<td>Negative</td>
<td>-0.12 (0.0086)</td>
<td>-0.14 (0.0010)</td>
<td></td>
</tr>
</tbody>
</table>
Summary

• Consistency across studies of aducanamab and donanemab on biomarkers and (mild) cognitive effects
• The ARIA “side-effects” mandate biomarker confirmation of treatment candidates and expensive monitoring
• Only for MCI/mild AD
• Tau markers emerging as key progression markers
• Expect increasing focus on identification of disease in what formerly preclinical state, in the context of primary care.
Disease-modifying medication
Symptomatic medication
Dementia-Friendly Community
Leverage Retained Strengths Compensation
Build Cognitive Reserve
Vascular health
Mental health/Social belonging/Purpose
Sleep/Nutrition/Exercise/Cognitive activity

Cognitive Age
Normal cognition
Subjective memory concerns
Mild cognitive impairment
Dementia

Primary Care, Biomarkers
Memory and Brain Wellness Center

2030
2020
1990
Visit the Memory Hub and the Frye Art Museum
Contribute your ideas, talent, and support

Volunteer with The Memory Hub:
Contact Mari Becker, Program Manager of Community Education & Impact
(206) 744-2017, mbecker1@uw.edu

Clinical appointments – Memory and Brain Wellness Center at Harborview
(206) 520-5000 “First call appointing”

Participate in a research study:
Contact Jessica McDougall, ADRC Lead Research Coordinator
(206) 744-0588, uwadrc@uw.edu
depts.washington.edu/MBWC

Questions?