Alzheimer’s Disease and Biomarkers

John H. Dougherty, Jr. M.D.
Medical Director
Cole Neuroscience Center
Dementia is a clinical syndrome characteristically marked by the insidious onset and slow progression of a cognitive impairment which impairs at least two areas of cognitive function. The cognitive impairment must also be severe enough to impair professional or social skills.

- For example: memory loss, impaired verbal fluency, impaired executive function, etc.
A Dementia can be either:

**Primary**

- or -

**Secondary**
Differential Diagnosis of Dementia

Vascular Dementias:
1. Multi-infarct dementia
2. SID, SVCVD (Binswanger’s disease)

Primary Dementias:
- Frontal lobe dementia
- Parkinson’s disease
- Progressive supranuclear palsy, others:

Diffuse Lewy Body Disease*

Vascular dementias and AD

AD and Lewy body dementias

5% 10% 65% 5% 7% 8%
MCI

- **Dementia** - abnormalities of at least two cognitive domains, impairment of professional and social skills.

- **MCI** - Mild cognitive impairment, Pre-dementia, usually abnormalities of only one cognitive domain, aMCI (amnestic mild cognitive impairment) no impairment of professional or social skills.
MCI

- ~8-9% convert to AD/ yr.
- ~40% are unchanged at one year
- ~20% are improved at one year

- Treatment with cholinesterase Inhibitors may slow conversion rate to dementia, and slow brain atrophy
Clinical Criteria

Alzheimer’s disease-

AD is suspected when there is no other primary or secondary cause to explain the dementing process and when the following criteria are present:

- Abnormal mental status as confirmed by objective criteria (ST, MMSE).
- The dementia is progressive.
- Wakefulness remains intact.
- There are abnormalities of at least TWO areas of cognition (ie: memory, speech, executive function, etc.).
- Few motor symptoms or signs (walking OK!)
- Frequently poor insight into cognitive deficits (anosognosia)

If the above criteria are adhered to one can be 85-90% confident that the clinical diagnosis of AD is correct.
New criteria for the diagnosis of Alzheimer's disease

- **MCI- Pre-Dementia**, minimal cognitive abnormalities, increased conversion rate to dementia.

- **Biomarkers- Pre-Clinical**, no clinical signs or symptoms of cognitive impairment.

- **Biomarker: definition**- Objectively measured and evaluated criteria, identifying specific brain pathology common to Alzheimer’s disease.
Biomarker Criteria:

A significant abnormality of episodic memory of at least 6 months duration

And, at least, one of the following

1. Temporal lobe atrophy on MRI
2. Abnormal FDG/PET-biparietal hypometabolism
3. Abnormal PET/CT amyloid imaging:
   - PiB(amyloid), FDDNP(TAU), *AV45- F18(amyloid)
4. CSF-(decreased beta-amyloid, increased tau)
5. Blood or serum analysis?

Neuroimaging and Dementia

- American Academy of Neurology Practice Parameter Guidelines recommend structural imaging in initial evaluation of patients with dementia

- Positron emission tomography (PET) of fluorodeoxyglucose (FDG) may help differentiate Alzheimer’s disease (AD) from frontotemporal dementia (FTD)

- Other PET imaging technologies are currently under development

MRI=magnetic resonance imaging; WM=white matter; PIB=Pittsburgh Compound-B; FDDNP=2-(1-{6-[2-[F-18]fluoroethyl](methyl)amino}-2-naphthyl)ethylidene)malonitrile

Decreased Connectivity by DTI
Alzheimer’s and Dementia, July 2008 Vol.4 p.265
John Dougherty and Yongxia Zhou

Green: PCC ROI
Red: Fiber tracts connecting ROI to the whole brain
Alzheimer’s Test Wins Expert Panel’s Approval

Alzheimer’s Test, First of Its Kind, Clears a Hurdle

BRAIN SCAN ENDORSED
AD Progression

- Pre-Symptomatic
- eMCI
- lMCI
- Dementia

Diagnostic Tools:
- CSF abeta42
- Amyloid Imaging
- FDG PET
- MRI Hippocampal Volume
- CSF Tau
- Cognitive Performance
- Function (ADL)
Vascular Risk Factors

Hypertension
- Hyperlipidemia
- Diabetes
- Obesity
- Smoking history

- TIA
- Hx: Strokes,
- CardiacDis./PVD
- Atrial fib or arrhythmias
Midlife cardiovascular risk factors and risk of dementia in late life

R.A. Whitmer, PhD; S. Sidney, MD; J. Selby, MD; S. Claiborne Johnston, MD; and K. Yaffe, MD

Abstract—Objective: To evaluate if midlife cardiovascular risk factors are associated with risk of late-life dementia in a large, diverse cohort. Method: The authors conducted a retrospective cohort study of 8,845 participants of a health maintenance organization who underwent health evaluations from 1964 to 1973 when they were between the ages of 40 and 44. Midlife cardiovascular risk factors included total cholesterol, diabetes, hypertension, and smoking. Diagnoses of dementia were ascertained by medical records from January 1994 to April 2003. Results: The authors identified 721 participants (8.2%) with dementia. Smoking, hypertension, high cholesterol, and diabetes at midlife were each associated with a 20 to 40% increase in risk of dementia (fully adjusted Cox proportional hazards model: HR 1.24, 95% CI 1.04 to 1.48 for hypertension, HR 1.26, 95% CI 1.08 to 1.47 for smoking, HR 1.42, 95% CI 1.22 to 1.66 for high cholesterol, and HR 1.46, 95% CI 1.19 to 1.79 for diabetes). A composite cardiovascular risk score was created using all four risk factors and was associated with dementia in a dose-dependent fashion. Compared with participants having no risk factors, the risk for dementia increased from 1.27 for having one risk factor to 2.37 for having all four risk factors (fully adjusted model: HR 2.37, 95% CI 1.10 to 5.10). Conclusion: The presence of multiple cardiovascular risk factors at midlife substantially increases risk of late-life dementia in a dose dependent manner.

NEUROLOGY 2005;64:277–281
DEMENTIA

Risk Factors

The study found that certain factors increased the risk of developing dementia 27 years later. The factors and how much they increased the risk were:

- High blood pressure 24 percent
- Smoking 26 percent
- High cholesterol 42 percent
- Diabetes 46 percent
SELF TEST II

Name: __________________________________________ Date: ______________________________

SIDE 1

Instruction #1:
Complete the questions in order. Complete each question before moving onto the next.
You may get help with instructions ONLY.

Questions:

1) In the space below, please draw the face of a clock and put the numbers in the correct positions.
   Now, draw in the hands at ten minutes after eleven.

2) Remember these words: (take a few minutes to commit them to memory)
   Telephone
   Police
   River

3) Write down the name of FIFTEEN animals.
   __________________________________________
   __________________________________________
   __________________________________________
   __________________________________________
   __________________________________________

Instruction #2:
Turn page over and keep it on Side 2.

SIDE 2

Instruction #3:
DO NOT return to Side 1.

Questions:

4) What are the three words you were asked to remember?
   __________________________________________
   __________________________________________
   __________________________________________

5) Circle each letter “Y” in the list of letters below.
   __________________________________________
   __________________________________________
   __________________________________________
   __________________________________________
   __________________________________________

6) What is the year?
   __________________________________________

   What is the month?
   __________________________________________

   What is the day of the week?
   __________________________________________

Thanks, you are finished!
The Computerized Self Test (CST): An Interactive, Internet Accessible Cognitive Screening Test For Dementia

Journal: Journal of Alzheimer's Disease
Publisher: IOS Press
ISSN: 1387-2877 (Print) 1875-8908 (Online)
Issue: Volume 20, Number 1 / 2010
DOI: 10.3233/JAD-2010-1354
Pages: 185-195
Subject Group: Neurosciences
Online Date: Wednesday, February 17, 2010
Computerized Cognitive Screening Test

Verbal Fluency – Animals

In the space below type the names of fifteen (15) animals. The keyboard will automatically appear. Use the cursor to click on each letter you wish to type, or you may use your keyboard.

Elephant was accepted 1/15

Ca1 2 3 4 5 6 7 8 9 0 delete
Q W E R T Y U I O P
A S D F G H J K L
Z X C V B N M
space

GO TO NEXT QUESTION
Cholinesterase Inhibitor Delays Conversion from MCI to AD (first 24 mo)

<table>
<thead>
<tr>
<th>MMSE Score (Changes from baseline)</th>
<th>12mo</th>
<th>24mo</th>
<th>36mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholinesterase Inhibitor</strong></td>
<td>-0.31+/-2.*</td>
<td>-0.98+/-2.*</td>
<td>-2.31+/-3</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>-0.80+/-2.</td>
<td>-1.49+/-2.</td>
<td>-2.75+/-4.</td>
</tr>
</tbody>
</table>

*P<0.05

Preventive Treatments in Alzheimer's Disease

Anti-oxidative agents: Vit.E, Folate, Fish+, omega-3 fatty acids etc.

Anti-inflammatory agents: NSAIDs?, etc.

Statins: Cholesterol Lowering Agents

Exercise: Physical and Mental
Positive Brain Effects of Walking in Healthy Aging

Positive Brain Effects of Walking in Cognitive Impairment
Long-term Effects of Cognitive Training on Everyday Functional Outcomes in Older Adults

Sherry L. Willis, PhD  
Sharon L. Tennstedt, PhD  
Michael Marsiske, PhD  
Karlene Ball, PhD  
Jeffrey Elias, PhD  
Kathy Mann Koepke, PhD  
John N. Morris, PhD  
George W. Rebok, PhD  
Frederick W. Unverzagt, PhD  
Anne M. Stoddard, ScD  
Elizabeth Wright, PhD  
for the ACTIVE Study Group

Context  Cognitive training has been shown to improve cognitive abilities in older adults but the effects of cognitive training on everyday function have not been demonstrated.

Objective  To determine the effects of cognitive training on daily function and durability of training on cognitive abilities.

Design, Setting, and Participants  Five-year follow-up of a randomized controlled single-blind trial with 4 treatment groups. A volunteer sample of 2832 persons (mean age, 73.6 years; 26% black), living independently in 6 US cities, was recruited from senior housing, community centers, and hospitals and clinics. The study was conducted between April 1998 and December 2004. Five-year follow-up was completed in 67% of the sample.

Interventions  Ten-session training for memory (verbal episodic memory), reasoning (inductive reasoning), or speed of processing (visual search and identification); 4-session booster training at 11 and 35 months after training in a random sample of those who completed training.

Main Outcome Measures  Self-reported and performance-based measures of daily function and cognitive abilities.

Results  The reasoning group reported significantly less difficulty in the instrumental activities of daily living (IADL) than the control group (effect size, 0.29; 99% confidence interval [CI], 0.03-0.55). Neither speed of processing training (effect size, 0.26; 99% CI, −0.02 to 0.51) nor memory training (effect size, 0.20; 99% CI, −0.06 to 0.46) had a significant effect on IADL. The booster training for the speed of processing group, but not for the other 2 groups, showed a significant effect on the performance-based functional measure of everyday speed of processing (effect size, 0.30; 99% CI, 0.08-0.52). No booster effects were seen for any of the groups for everyday problem-solving or self-reported difficulty in IADL. Each intervention maintained effects on its specific targeted cognitive ability through 5 years (memory: effect size, 0.23 [99% CI, 0.11-0.35]; reasoning: effect size 0.26 [99% CI, 0.17-0.35]; speed of processing: effect size, 0.76 [99% CI, 0.62-0.90]). Booster training produced additional improvement with the reasoning intervention for reasoning performance (effect size, 0.28; 99% CI, 0.12-0.43) and the speed of processing intervention for speed of processing performance (effect size, 0.85; 99% CI, 0.61-1.09).

Conclusions  Reasoning training resulted in less functional decline in self-reported IADL. Compared with the control group, cognitive training resulted in improved cognitive abilities specific to the abilities trained that continued 5 years after the initiation of the intervention.

Trial Registration  clinicaltrials.gov Identifier: NCT00298558
Healthcare Crisis Today

- At present 4 million people in the United States have AD.
- 60% of all nursing home admissions are the result of a dementing illness, most commonly AD.
- AD is the sixth leading cause of death in the United States.
- The total lifetime cost of care for a patient with AD is estimated to be in excess of $174,000.
- The total cost of care in the United States for patients with AD is currently estimated to be >$100 Billion.
Alzheimer’s disease and the Healthcare Crisis

• As many as 60% of the patients with AD may go undiagnosed in the primary care setting 1

• As many as ~40% of the diagnosed patients may not receive pharmacologic treatment 2

• 1 Knopman et.al. Journal American Geriatrics Society 2000;48: 300
• 2 Datamonitor 2002
Forecast of Alzheimer’s Disease Prevalence in the U.S.

<table>
<thead>
<tr>
<th>Year</th>
<th>65-74 Years</th>
<th>75-84 Years</th>
<th>85+ Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>4.5 Million</td>
<td>4.5 Million</td>
<td>4.5 Million</td>
</tr>
<tr>
<td>2030</td>
<td>7.7 Million</td>
<td>7.7 Million</td>
<td>7.7 Million</td>
</tr>
<tr>
<td>2050</td>
<td>13.2 Million</td>
<td>13.2 Million</td>
<td>13.2 Million</td>
</tr>
</tbody>
</table>

Alzheimer's disease usually develops slowly, taking many years to get to the point where symptoms become noticeable and Alzheimer’s disease is most common in the elderly population.

If we could delay the onset of AD for 5 years, we would in effect reduce the number of patients with Alzheimer’s disease by one half

(We can currently delay the symptoms of Parkinson’s disease, 3-5yrs)

(AD prevention and evidence based medicine)