Alzheimer’s Prevention and Treatment: Where Are We Headed?

19th Annual Updates on Dementia
May 11th 2017

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Stanford University

Development of Alzheimer’s

Amyloid plaques  Tau tangles

Age-related cognitive impairment  Mild cognitive Impairment (MCI)  Dementia
Dementia risk factors

- Genetics
- Lack of physical exercise
- ‘Western’ diet
- Medical conditions (HTN, diabetes)
- Sleep apnea
- Anti-cholinergic medications
  (Benadryl, Paxil, Elavil, Ditropan)

Alzheimer’s Genetics

Sporadic AD (> 98%) onset > 65 yo
Familial AD (< 2%) onset 40-50s

Sporadic: Many genes + environment

ApoE gene: ApoE2 / ApoE3 / ApoE4

<table>
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<th>No family hx:</th>
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<td>Lifetime risk 15%</td>
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<tr>
<th>No family hx:</th>
<th>One parent with AD:</th>
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<tr>
<td>Lifetime risk 15%</td>
<td>E3/E3: 30%</td>
</tr>
<tr>
<td>- E4 9%</td>
<td>E3/E4: 45%</td>
</tr>
<tr>
<td>+ E4 30%</td>
<td>E4/E4: 60%</td>
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</table>

April 2017: FDA approves 23 and me ApoE testing

Mike Greicius at Stanford: ‘protective’ genes

Making a dx of Alzheimer’s

- History
- Physical exam
- Cognitive exam
- Brain MRI
- Blood: B12, thyroid, others

~ 85% accurate
Amyloid and tau detection with PET scans
Amyloid and tau detection with PET scans

20 yrs pre symptoms
1/3 positive age 70

MRI

Amyloid PET

Alzheimer's

Normal

MRI

Amyloid PET

Tau PET

Alzheimer's

Normal
Imaging brain circuit function

Resting state fMRI

Healthy elderly
Early Alzheimer’s

FDA approved therapies

Do not delay onset or slow progression

• Donepezil (Aricept)
• Rivastigmine (Exelon)
• Galantamine (Razadyne)

• Memantine (Namenda)

• Namzaric = donepezil + memantine
Prevention Strategies

Cognitive exercise

Sleep

Diet

Physical exercise

www.lumosity.com

www.brainhq.com

Scientific evidence does not support the brain game claims, Stanford scholars say

Sixty-nine scientists at Stanford University and other institutions issued a statement that the scientific track record does not support the claims that so-called “brain games” actually help older adults boost their mental powers. [Stanford Report 2014]

Are “brain games” effective?

Mowszowski et al; Neuropsychol Rev 2016

11/13 studies, healthy aged: improved executive function

However:

• Minimal or no generalization
• Effects in MCI cognition/progression not known
Video game training enhancing cognitive function in older adults

NeuroRacer 1 hour 3x/week for 1 month

6 months: improved working memory in multitask group

Commercial version under development

Mediterranean diet and cognition

13/18 studies associated with:
- decrease conversion to AD
- improved cog fxn (memory, executive fxn)

Reduced shrinkage of hippocampus

52 yo Med Diet 50 yo Western Diet

~20% risk reduction
Diet / Supplements

**Vitamin E**
- Mild/mod Alzheimer’s 2000 IU/d: 19% reduction rate decline ADLs; no cog effects (Dysken et al, 2014)
- Normal elderly; 400 IU/day: PREADVISE trial (2017) – no effect

**Vitamin D**
- ‘normal’ level (controversial) 20-40 ng/mL
  - < 10 ng/mL: 2.2X; < 20 ng/mL: 1.5X increased risk
  - 3 small interventional studies: improved executive function (1-15 mo)

**Sleep ?**

Sleep–disordered breathing:
- 1.9X odds MCI at 5 yrs (*JAMA* 2001)
- 1.7X odds dementia at 5 years (*PLoS One* 2013)
Sleep disruption prevents normal morning Aβ decrease

Human intrathecal catheter monitoring CSF amyloid levels

Spira et al JAMA Neurol 2013

Sleep, amyloid and Alzheimer’s

Sleep duration: <6h  6-7h  >7h

Amyloid PET

Prospective trials possible?

Spira et al JAMA Neurol 2013
Exercise and dementia risk

Exercise – how much? 30 min/day 5d/week - moderate levels

16 studies, highest vs lowest exercise levels: 45% reduced risk AD
(Hamer and Chida, Psychol Med, 2009)

15 prospective cohort studies, 1-12 yrs f/u 35-38% reduced risk, low-moderate / high levels exercise.
(Sofi et al, J Int Med 2011)

17 studies, highest vs lowest exercise levels: 40% reduced risk AD
(Guure et al, BioMed Res Int 2017)

~40% reduced risk
Exercise and decreased amyloid accumulation

45-88 yo normals – parent-AD ± exercise past 10 years

Exercisers:
➢ 30 min mod exercise 5d/wk (AHA)

Head et al Arch Neurol 2012
Walking – Reversal of Hippocampal
Age-related Atrophy

10 40 min/day walk 1 year

hippocampus
1-2%/yr atrophy

Mechanism? BDNF?

Erickson et al
PNAS 2011
Exercise effects on cognition in dementia

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD</th>
<th>CI</th>
<th>N</th>
<th>SMD</th>
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<td>Arencorva (2014)</td>
<td>0.84</td>
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<td>Rosser (2013) [1]</td>
<td>0.45</td>
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<td>Cott (2002)</td>
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<td>Eggemont (2009a)</td>
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<td>Hokkens (2008)</td>
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<td>Holthoff (2012)</td>
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<td>-0.28-1.06</td>
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<td>Kemoe (2010)</td>
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<td>0.15-1.83</td>
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<td>Kwak (2010)</td>
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<td>0.27-1.79</td>
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<td>* Miu (2008)</td>
<td>-0.36</td>
<td>-0.96-0.29</td>
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<td>Strandberg (2009)</td>
<td>0.26</td>
<td>-0.46-0.98</td>
<td>27</td>
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<td>Stevens (2006)</td>
<td>0.98</td>
<td>0.38-1.50</td>
<td>45</td>
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<tr>
<td>* Versarudi (2011) †</td>
<td>3.06</td>
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<td>Visagiedl (2012)</td>
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<td>Yildiz (2011)</td>
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<td>Overall random</td>
<td>0.42</td>
<td>0.23-0.62</td>
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Greater than drug effect


Exercise and life-long brain health

Higher-fit children:
- Academic achievement
- Better cognitive control, flexibility
- Larger brain structures

Swedish military draft, cycle ergometer test at age 18
~40 years later:

Low fitness ➔ 2.5X early-onset dementia

Nordstrom et al JAMA IM 2013
Summary: Prevention/Rx Strategies

Cognitive exercise:
No clear epi Effects on Exec Fxn
No risk reduction

Diet:
Lots epi ~20% risk dec
No RCTs

Physical exercise:
Lots epi ~40% risk dec
Multiple RCTs (goal 30 min/5 days)

Sleep:
Early epi, ~25% inc risk?
No RCTs

Supplements:
O3FAs, Vit D

www.lumosity.com
www.brainhq.com

Future: combination approaches
(FINGER – Finnish Geriatric Intervention Study)

Current Alzheimer’s trials

Antibodies, drugs to decrease amyloid or tau accumulation

- Phase 3 amyloid trials in mild-moderate Alzheimer’s: failed
- Phase 3 amyloid trials in early/mild Alzheimer’s: ongoing
- Tau trials in phase 1-2
Focused ultrasound for AD treatment

Focused ultrasound in AD mice reduces amyloid plaque load

Illustration – Amanda Buch, Columbia University

sham ultrasound

Phase 1 safety trial underway
Leinenga and Götz
Science Translational Med, 2015

Young blood plasma into old mice

Villeda et al Nature Med 2014

Phase 1 clinical trial at Stanford for safety completed
Developing a more powerful drug – addressing multiple mechanisms

Small molecules inhibit amyloid/tau/aging mechanisms to reverse degeneration

Longo Lab, Stanford
The Drug Pipeline and ‘Valley of Death’

Target discovery
Leads
mice

University Lab

-rat/dog safety -FDA
P 1 safety normals
P 2a AD

Small Biotech

P 2b AD
P 3 AD

Pharma

Phase 1 safety trial: LM11A-31-BHS

1 site / 72 subjects
Phase 2a trial: LM11A-31-BHS

4 countries / 12 sites / 120 subjects (first dosing January 2017)

Brain Health

Precision Health:
• Genetic/risk factor assessment
• Tailored prevention/life strategies
• Biologically potent therapies
Stanford Alzheimer’s Disease Research Center (ADRC)

- **GOALS:** Understand AD and related disorders; enable earlier detection; develop more effective approaches to prevention and treatment.

- **WHO:** Volunteers with Alzheimer’s disease, Parkinson’s disease, Lewy body disease, or Mild Cognitive Impairment. Especially interested in enrolling Latino families.

- **WHERE:** Testing is done at Stanford Health Care

- **COMMITMENT:** Testing involves 2 to 3 days; needed visits may be spread out over a period of up to 3 months.

- **CARE PARTNERS:** Enroll family or friends who are care partners to the person with dementia whenever possible. We offer free classes in caregiver stress management at community locations through the year.
Contact Information for Referrals

- Bilingual, bicultural staff will respond to questions and assist in conducting all screenings and actual evaluations.

- For more information, call Christina Wyss-Coray, RN, BSN, PHN at (650) 721-2409 or email us at ADRCstanford@stanford.edu. Although she is not bilingual, she will refer the call to appropriate staff for follow-up.

- Appointments are now being scheduled so please feel free to contact us.

- If you have questions about the suitability of a possible referral, please call.

- Dementia Awareness Campaign in Latino Communities: Dr. Ann Bilbrey: abilbrey@stanford.edu / 650 498-5903
- Information in Spanish: Nusha Askari 650 721-5283
  adrcstanford@Stanford.edu

- Exercise and wellness classes
- Support services; travel reimbursements, participation incentives.