What We Can Do To Prevent or Reduce the Risk for Dementia

Colloquium on Health and Wellness
October 10th, 2018

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Cognitive health span

- Normal cognition
- Age-related cognitive impairment
- Mild cognitive impairment (MCI)
- Dementia

Amyloid plaques, Tau tangles

- Alzheimer’s disease
- Vascular dementia
- Lewy body dementia
Synapses / Spines

axon

dendrites

spines

synapse

A

normal spines

B

aging / Alzheimer’s
Dementia now stands along cancer as one of the greatest enemies of humanity. The cost to society and to the individuals and families affected are staggering.

- David Cameron
Prevalence of Alzheimer’s disease


‘Health span’ vs ‘life span’
Dementia risk factors

- Genetics
- Sedentary lifestyle
- ‘Western’ diet
- Medical conditions (HTN, diabetes)
- 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>
<thead>
<tr>
<th>No family hx:</th>
<th>One parent with AD:</th>
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<tbody>
<tr>
<td>Lifetime risk 15%</td>
<td>E3/E3: 30%</td>
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<tr>
<td>- E4 9%</td>
<td>E3/E4: 45%</td>
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<tr>
<td>+ E4 30%</td>
<td>E4/E4: 60%</td>
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April 2017: FDA approves 23 and Me ApoE testing

Mike Greicius at Stanford: ‘protective’ genes
Tom Sudhof at Stanford: how ApoE4 increases risk
Dementia diagnosis

- History (dementia onset)
- Physical exam
- Cognitive exam
- Brain MRI
- Blood: B12, thyroid, others

- \(~85\%\) accurate
- Need earlier diagnosis
Amyloid and tau detection with PET scans

20 yrs pre symptoms
1/3 positive age 70

MRI

Amyloid PET

Tau PET

Alzheimer’s

Normal
Combination MRI – PET scan
Imaging brain circuit function

Resting state fMRI

Healthy elderly

Early Alzheimer’s

Mike Greicius
Stanford
FDA approved therapies

Do not delay onset or slow progression

- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)
- Memantine (Namenda)
Computerized cognitive training: healthy aging

Mowszowski et al; Neuropsychol Rev 2016
11/13 studies, healthy aged: improved executive function
However: minimal transfer effect - other domains, activities of daily living (ADLs)

Shah et al, Neuropsychol Rev 2017
Level I (at least 2 well designed RCTs): Posit, Cognifit (QL/IADLs)

- Significant effects in cognitive domains, QL measures, IADLs
- Effects on progression to MCI/dementia not known
Lumosity to Pay $2 Million to Settle FTC Deceptive Advertising Charges for Its “Brain Training” Program

Company Claimed Program Would Sharpen Performance in Everyday Life and Protect Against Cognitive Decline

FOR RELEASE

January 5, 2016
Purpose in life - effect on dementia

Rush Memory and Aging Project
Prospective longitudinal aging study in senior housing facilities in Chicago

Boyle et al
Arch Gen Psych 2010
Systematic reviews longitudinal and prospective trials: MedDiet and cognition

13/18 longitudinal studies associated with:
- slowed decline
- decrease conversion to AD
- improved cog fxn: memory, executive, visual

Abbatecola et al - Curr Opin Clin Nutr Metab Care 2018
- Med diet
- DASH (dietary approach to systolic hypertension)
- MIND (Mediterranean-DASH diet intervention for neurodegenerative delay)

~20% risk reduction
Med diet effects in older adults without cognitive impairment

Meta-analysis and review of 15 cohort studies: Loughrey et al Adv Nutr 2017

Episodic memory

Global cognition

Semantic memory

Two prospective trials:
PREDIMED: RCT 6.5 y – subjects -high vascular risk; MD + EVOO vs low fat diet
- higher cog performance multiple domains
- decreased MCI
Martizez-Lapiscina et al JNNP 2013

MD + EVOO or nuts vs low fat diet
- Improved verbal learning and executive function with EVOO
Valls-Pedret et al, JAMA Intern Med 2015
**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

**Vit 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)

**Omega-3 FA**
- AD 5/6 studies *no* effect except 1 study (mild AD subgroup) Thomas et al, BioMed Res 2015
- MCI 4/5 small studies mild improvement;
- Normal aging: *no* effect (3/3 studies); Jiao et al, Am J Clin Nutr 2014
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

Amyloid levels

disrupted sleep

normal sleep

Ooms et al  JAMA Neurology 2014
Sleep, amyloid and Alzheimer’s

Sleep duration:

- <6h
- 6-7h
- >7h

Amyloid PET

Prospective trials possible?

Spira et al
JAMA Neurol 2013
Exercise ?
Exercise and dementia risk

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)

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

~40% reduced risk
Good quality evidence – exercise for promotion of cognitive brain health in older adults.

Exercising ≥ 52 hours/25 weeks in sessions lasting ~ 1h associated with improved cognition in older adults with and without cognitive impairment.

Individuals can participate in aerobic, resistance (strength) training, mind–body exercises, or combinations of these interventions.

Improvements in processing speed/attention, executive function, and global cognition are most stable and consistently associated with exercise.
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

Mechanism? BDNF?

Erickson et al. PNAS 2011
Exercise effects on cognition in MCI

Results in dementia are mixed
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

No prevention evidence for current drugs

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

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

**Diet:**
- Lots epidemiology
- ~20% risk dec
- No RCTs

**Supplements:**
- O3FAs, Vit D

**Cognitive exercise:**
- No clear epidemiology
- Effects on Exec Fxn – transfer effect?

www.lumosity.com
www.brainhq.com
Future: combination approaches (FINGER – Finnish Geriatric Intervention Study)

Kivipelto and Hakansson
Sci American 2017

Enrolled age 60-77 normals at higher risk for cog decline

- Nutrition
- Exercise
- Cognitive training
- Monitoring/management

vs

- Regular health advice
Developing better therapies for prevention and treatment
Alzheimer’s Prevention Trials

Alzheimer’s Prevention Initiative, Medellin, Colombia

Dominantly Inherited Alzheimer’s Network (DIAN)

A4 Trial (Amyloid Treatment in Asymptomatic Alzheimer’s)
> 70 yo; amyloid PET-positive; no dementia
Trials targeting amyloid or tau

- Phase 3 amyloid trials in mild-moderate Alzheimer’s: failed
- Phase 2 and 3 amyloid trials in MCI/mild Alzheimer’s: ongoing
- Tau trials in phase 1-2

Antibodies, drugs to decrease amyloid or tau accumulation

Aducanumab (Biogen-Idec) MCI-mild AD; Nature 2017
Eisai-Biogen amyloid antibody BAN2401

Top Two Doses vs Placebo

Change in cognitive score vs months

- Placebo
- 10 mg/kg monthly
- 10 mg/kg bi-weekly

Red line shows projected 25% less decline vs placebo over time (protocol defined)

High dose (excludes apoE4)
Placebo (includes apoE4)

47% reduction
P=0.017
Young blood plasma into old and AD mice

Tony Wyss-Coray
Stanford Neurology

Phase 1 clinical trial at Stanford for safety completed; results reported November 2017

Young vs old blood plasma – what is the difference? ‘Fountain-of-youth’ ingredient?

Villeda et al Nature Med 2014
Alzheimer’s therapy: blocking amyloid, tau, aging and inflammatory effects

- Aβ:
  - dystrophy
  - spine loss
  - LTP loss
  - tau-o

- tau:
  - spine loss
  - LTP loss

- aging:
  - neuronal atrophy
  - neurite degen

- microglia:
  - MG activation

TSPO PET
James et al
Theranostics 2017

neuron / synapse dysfunction-degeneration
Small molecules inhibit amyloid/tau/aging mechanisms to reverse degeneration

Normal mouse

AD mouse

AD mouse + drug

LM11A-31-BHS:  mouse  →  human

Longo Lab, Stanford
CT-PET detection of brain inflammation

Michelle James / Sam Gambhir / Frank Longo Stanford

normal mouse  AD mouse + placebo  AD mouse + test drug
Testing Alzheimer’s Therapies
The Drug Pipeline and ‘Valley of Death’

University Lab
- Target discovery
- Leads
- Mice

Small Biotech
- Rat/dog safety - FDA
- P 1 safety normals
- P 2a AD

Pharma
- P 2b AD
- P 3 AD
Phase 2a trial: LM11A-31-BHS in Alzheimer’s subjects

5 countries / ~20 sites / 180 subjects

2020 results
Barcelona Alzheimer’s Treatment and Research Center
Developing a more powerful drug – addressing multiple mechanisms
Brain Health

Precision Health:
• Genetic/risk factor assessment
• Tailored prevention/life strategies
• Biologically potent therapies