The Coming Epidemic of Late-Life Cognitive Impairment

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Late life cognitive impairment

- **Magnitude**
  - Cognitive impairment (CIND, MCI)
  - Dementia

- **Diagnosis**
  - Alzheimer disease
  - Cerebrovascular disease

- **Prevention is the best treatment**
Three phases of cognitive impairment

- **Preclinical**
- **CIND**
- **Dementia**

Courtesy Lon Schneider, M.D., University of Southern California
Prevalence of Alzheimer Disease
5 million in 2010, 10 million in 2040

Women have higher life-time risk of dementia, Alzheimer and stroke.

Note: Before age 75 men have higher risk of stroke,
For each person with Stroke or Dementia, there is another with CIND (Canadian Study of Health and Aging).


Women at higher risk of dementia
Vascular Brain Injury seen by T-2 weighted MRI:
Infarcts, white matter changes, and hemorrhage

Major artery infarcts

Small artery infarcts
   Lacunar infarcts
   Silent vs. symptomatic

White matter hyperintensities

Microbleeds
   T2*-weighted gradient echo planar
Misfolded Proteins and Amyloid Fibrils in Neurodegenerative Disorders

Alzheimer Disease (AD) (Amyloid β; tau)

Fronto Temporal Dementia (FTLD) (tau or TDP-43)

Parkinson Disease (PD, DLB) (α-synuclein Lewy bodies)

Prion Disease (CJD) (Prion deposits)

Huntington Disease (HD) (Huntingtin deposits)
Future:
Infarcts on MRI for VCI
Amyloid PET Retention for AD

Rabinovici GC. Presented at Human Amyloid Meeting, Toronto, 2010
Aging Brain Program Project
50% of Older Adults with Dementia have **Mixed Pathology** (i.e., Multiple Neuropathologic Diagnoses)

Additive effects of cerebral infarction and AD pathology on risk for dementia
(Religious Orders Study n=153)

Schneider et al. Neurology 2004; 62: 1151
Growing AD portfolio with increasing severity of cognitive impairment

Prevention is best treatment
Subcortical Ischemic Vascular Disease (SIVD, S-CVD)

Silent infarcts in 24% of population –

Lacunes:
Silent and symptomatic

White matter hyperintensities
Primary Prevention

- Brain at risk
- Prevent infarction
- What to do about Apo E4 genotype?

Manage vascular risk factors
- HTN*
- Diabetes
- Hyperlipidemia
- Heart disease

*Risk of stroke double for every 20/10 mm increase in BP over 115/75
ApoE4

ASCVD + apo E4: 3.9

Homo cysteine

DM

HTN

Large Artery - IMT

3.0

AD

PV WML?

SBI WML

“Silent”

Breteler MMB. Ann NY Acad Sci 2000;903:457
Brain Injury

Cholesterol

Vascular Risk Factors

ApoE4

Genes

Path

Brain Injury

Signs/Sx

Risks of Cognitive Decline

DM

DM x one E4: -4.4
DM x two E4: -9.05

Hi Chol x one E4: -3.19
Hi Chol x two E4: -6.27

Atherosclerosis Risk in Communities (ARIC)


Multiple regression analysis

ApoE4

No E4: -2.51
E4/--: -3.2
E4/E4: -4.54

Cognitive Decline

Digit Symbol Substitution
Evidence favors effectiveness of treatment for hypertension in prevention of cognitive impairment

<table>
<thead>
<tr>
<th>Study</th>
<th>Active (N/n)</th>
<th>Placebo (N/n)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROGRESS RR¹²</td>
<td>3051/193</td>
<td>3054/217</td>
<td>0.89 (0.74–1.07)</td>
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<tr>
<td>Syst-Eur RR¹⁰</td>
<td>1238/11</td>
<td>1180/21</td>
<td>0.50 (0.25–1.02)</td>
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<tr>
<td>SHEP RR¹⁴</td>
<td>2365/37</td>
<td>2371/44</td>
<td>0.84 (0.55–1.30)</td>
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<tr>
<td>HYVET RR</td>
<td>1687/126</td>
<td>1649/137</td>
<td>0.90 (0.71–1.13)</td>
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<tr>
<td>Combined (random)</td>
<td></td>
<td></td>
<td>0.87 (0.76–1.00)</td>
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</tbody>
</table>

Cochran Q=2.409; p=0.491
Test for overall effect; p=0.045
**Physical activity decreases risk of VaD**

<table>
<thead>
<tr>
<th>Walking, Kcal/wk</th>
<th>Cases, n (%)*</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;417 (n = 239)</td>
<td>0</td>
<td>0.27 (0.12-0.63)</td>
<td>0.37 (0.16-0.87)</td>
<td>0.36 (0.15-0.87)</td>
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<tr>
<td>209-417 (n = 304)</td>
<td>10 (1.8)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;209 (n = 206)</td>
<td>17 (18.2)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Values are hazard ratio (95% CI). Model 1 is adjusted for age, gender, education, and APOE genotype. Model 2 is adjusted as Model 1 + cardiovascular disease, hypertension, and hyperhomocysteinemia. Model 3 is adjusted as Model 1 + comorbidity and basic activities of daily living motor disability.

*Except when otherwise indicated, HRs for vascular dementia refer to the highest and middle tertiles pooled together compared to the lowest tertile.*
What must we do?

- Research to crack the AD code.

- Healthy lifestyle: Prevent vascular contributions to cognitive impairment.