Aging and Cognitive Change

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Outline

• Population
• Underlying pathologic processes
• Therapies
• Public Health Implications
Population

- “Aging”
- ? Normal
- Underlying disease
Underlying Pathologies

• Vascular disease
• AD
• Lewy Body dementia
• White Matter abnormalities
• Others
Vascular risk factors and cognition

• Epidemiologic studies have demonstrated associations between:
  – Stroke risk (and stroke) and cognitive decline
  – Hypertension and cognitive performance
  – Diabetes and cognitive decline
  – Smoking and cognitive performance
What do we mean by “vascular disease”?

• Vascular contributions to dementia include:
  – Vascular risk factors (hypertension, diabetes, smoking, high cholesterol)
  – Microvascular markers (retinal microvascular changes)
  – Macrovascular markers (carotid artery disease)
  – Clinical strokes
  – Radiographic changes
    • Brain infarcts
    • White matter ischemic changes

from Vermeer et al., Lancet Neurology 2007; 6(7): 611-619
Histopathology of leukoaraiosis

- Perivascular demyelination and gliosis
- Dilated Virchow-Robin spaces
- Small lacunae
- Axonal loss, loss of glial cells
- Myelin rarefaction (sparing U fibers) with spongiosis
- Evidence for both vascular and demyelinating mechanisms

Adapted from Chimowitz et al., *Arch Neuro.*, 1992, 49: 747-752)
Prevalence of Silent Brain Infarcts: Rotterdam Study

- N = 1,077
- 60 - 90 years
- N = 217 (20%) w/ clinically asymptomatic infarcts
  - female > male
  - age
  - hypertension

Vermeer SE et al. STROKE 33:21-25, 2002
White matter disease epidemiology

• Rotterdam study:
  – Among 2000 participants, median white matter lesion volume was 1.8 mL (45-59 yo), 3.1 (60-74 yo), and 7.7 mL (75-97 yo)
  – Only 8% of individuals 60-90 had no subcortical white matter lesions, 20% had no periventricular lesions, and 5% had neither. (de Leeuw et al., *JNNP* 2001; 70(1): 9-14).

• Atherosclerosis Risk in Communities (ARIC) study
  – 17% of individuals 50-71 yo had a white matter disease grade of 0, median volume was 9.1 mL (range 0-90 mL) at age 61-83 yrs (Unpublished)
Dementia and vascular disease

• The diagnosis of “vascular dementia” as a pure entity is probably quite rare
• Many patients diagnosed with AD may actually have some vascular contribution, and patients diagnosed with vascular dementia may have some contribution from AD neuropathology
Cognitive Change after Coronary Bypass Surgery

- Should Cognitive Change Influence choice of therapy?
Prospective, 6 year comparison of:

Cognitive evaluation at:
  – Baseline, 3 mos, 1 yr, 3 yrs and 6 yrs
  – 22 tests to 8 cognitive domains

Mortality (10 years)
## COCAD Study – Comparison of All 4 Study Groups at 6-Year Follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>CABG (n=152)</th>
<th>OPCAB (n=75)</th>
<th>NSCC (n=99)</th>
<th>HHC (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>17%</td>
<td>24%</td>
<td>19%</td>
<td>4%</td>
</tr>
<tr>
<td>Completed Testing</td>
<td>76%</td>
<td>75%</td>
<td>80%</td>
<td>91%</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>71.2</td>
<td>70.4</td>
<td>71.9</td>
<td>67.6</td>
</tr>
<tr>
<td>Taking a statin drug</td>
<td>85%</td>
<td>77%</td>
<td>75%</td>
<td>12%</td>
</tr>
<tr>
<td>Mean Mini-Mental</td>
<td>27.4</td>
<td>28.5</td>
<td>28.0</td>
<td>28.6</td>
</tr>
<tr>
<td>Mini-Mental &lt;24</td>
<td>7%</td>
<td>2%</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Mean CES-D score</td>
<td>9.5</td>
<td>11.3</td>
<td>9.0</td>
<td>6.0</td>
</tr>
<tr>
<td>CES-D &gt;15</td>
<td>15%</td>
<td>21%</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>
Late Decline in Cognitive Function

- **Does occur**
  - Not specific to bypass-pump
  - Occurs in all groups with coronary artery disease
- **Slight decline in heart healthy controls**
- **Mechanisms**
  - Progressive vascular disease
  - Other pathologies
  - Age
Prevalence of silent infarcts in candidates for CABG (N=421)

## Outcomes Following Coronary Surgery (CABG)

<table>
<thead>
<tr>
<th>Prior MRI findings</th>
<th>CVA</th>
<th>NP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal [$n=212$]</td>
<td>1.4%</td>
<td>7%</td>
</tr>
<tr>
<td>Small infarcts [$n=126$]</td>
<td>5.6%</td>
<td>13%</td>
</tr>
<tr>
<td>Multiple infarcts [$n=83$]</td>
<td>8.4%</td>
<td>20%</td>
</tr>
</tbody>
</table>

$N=421$

Goto T et al. 2001
Underlying Pathologies

- Vascular disease
- AD
- Lewy Body Dementia
- White Matter abnormalities
- Others
  - Tau
  - Loss of REST (neuron-restrictive silencer factor)
  - Inflammation
FIGURE 2: Contributions of combinations of the pathologic indices to cognitive decline (model-derived slopes). AD = Alzheimer disease. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]
FIGURE 3: Variation in cognitive decline explained by the pathologic indices (gray) and the residual, unexplained variation in cognitive decline (white) derived from fully adjusted models. AD = Alzheimer disease; CVD = cerebrovascular disease; LBD = Lewy body disease.
Tau in Elderly brain
Brad Hyman-personal communication

- Present in all brains
- Entorhinal Cortex
- Age related
- Clinically irrelevant
  - Similar to cholesterol plaque in coronary artery
  - Evidence of prostate cancer at autopsy
Underlying Pathologies

- Vascular disease
- AD
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- White Matter abnormalities
- Others
  - Tau
  - Loss of REST (neuron-restrictive silencer factor)
  - Inflammation
Therapies

• Rx
  – Treatment of known pathologies
  – Treatment of cognitive decline

• Exercise
  – Mechanism-?

• Brain Training
Hypertension and cognition

- Strongest associations with cognitive endpoints are from *midlife* hypertension
  - Freitag et al., *Stroke* 2006: Midlife pulse pressure associated with incident dementia cases (Honolulu-Asia Aging Study)
  - Kivipelto et al., *BMJ* 2001: Elevated midlife blood pressure or cholesterol associated with Alzheimer’s disease later in life
  - Petrovitch et al., *Neurobiology of Aging* 2000; Midlife blood pressure is associated with neuritic plaques, neurofibrillary tangles and brain weight at autopsy
Midlife >> later life vascular risk factors are strongly associated with clinical dementia

• Freitag et al., *Stroke* 2006: Midlife pulse pressure associated with incident dementia cases (Honolulu-Asia Aging Study)

• Kivipelto et al., *BMJ* 2001: Elevated midlife blood pressure or cholesterol associated with Alzheimer’s disease later in life

• Ott et al., *Neurology* 1999; Diabetes associated with AD dementia (RR 1.9; Rotterdam Study)

• Crane et al., *NEJM* 2013; Higher blood glucose associated with increased risk of dementia (even in nondiabetics)- Adult Changes in Thought study
Clinical trials: HTN and cognition

• Clinical trials have failed to show strong protection from antihypertensive drug use:
  – ACCORD-MIND (Williamson et al., *JAMA Int Med* 2014): Intensive BP control (SBP<120 mm Hg) in diabetics over 40 months showed no benefit for cognitive decline (but more atrophy!)
  – Most other RCT’s have not showed cognitive benefit of BP control
  – PROGRESS trial (perindopril) did show reduction in cognitive decline among stroke/ TIA patients over only 3.9 years
Summary of Data regarding Hypertension and the Brain

• In prevention of stroke, lower blood pressure appears to be better

• There is a possibility that lower BP, especially in particular patient groups or in older persons, might be associated with adverse outcomes.

• Hypertension, especially in midlife, is associated with more microvascular disease of the brain, shown by leukoaraiosis and more cognitive decline/ dementia

• Clinical trials have failed to support a reduction in adverse cognitive/ brain imaging endpoints associated with BP reduction, likely due to requisite long followup
Treatment of cognitive decline

• Brain Training
  – Widely Used (Big Bucks)
    • Inordinate claims-”normal aging”, AD
  – Specific effects
  – Transfer
  – Neurologic basis
    • Recruitment of new brain mechanisms (stroke)
    • Expansion of existing mechanisms
Brain Training Needs Research

- Multi-modal
- Utilize cognitive flexibility
- Novelty
- Individualize
- Brain imaging
Medications

• Medication Cognitive Enhancement
  – Short-term
    • Modafinil (Provigil
  – Long-Term
    • ?
Public Health Issues

• Decision-Making
• Susceptibility
  – Financial
  – Therapeutic