Vascular contributions to dementia:
A path to prevention

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What is Vascular Dementia?

• Also called “Multi-infarct dementia”; other types include subcortical vascular dementia, genetic vascular dementias (CADASIL)
• Classically defined as rapid onset, stepwise progression of symptoms
  – Sometimes occurring after a stroke, but often not
  – Diagnosis requires cognitive disorder AND either clinical stroke or brain vascular disease by neuroimaging (Gorelick et al., 2011)
• Patients often have problems with attention and executive function; memory may not be affected
• Clinically it is the second leading cause of dementia (~20% of dementia cases), occurring in 14.6 per 1000 person-yrs (vs 19.2 for AD) (Fitzpatrick et al., 2004)
Vascular contributions to dementia may be relevant in a much larger percentage of patients with dementia

Vascular dementia  
Alzheimer’s disease

Mixed dementia

Vascular and AD overlap: Autopsy evidence

• Between 55-80% of AD patients have coincident vascular changes in the brain (Bangen et al., Alzheimers & Dementia 2015; Toledo et al., Brain 2013)

• Multiple studies have found less AD neuropathological changes (plaques, tangles) in patients with vascular changes for an equivalent level of cognitive impairment

Modified from Toledo et al, Brain 2013
(VP: Vascular Pathology; AD: Alzheimer’s Disease)
Possible explanations for a vascular/AD connection

- Vascular disease and Alzheimer’s changes are additive, leading to worse cognition when both are present, OR
- Vascular disease directly leads to AD neuropathological changes

Mechanisms for a vascular/AD interaction

- Vascular risk factors lead to alterations in cerebral blood vessels and can lead to low cerebral blood flow, especially in the white matter of the brain
- The blood brain barrier can be disrupted in the presence of vascular disease
- Role of the neurovascular unit: Amyloid-β itself may directly damage blood vessels, further worsening cerebral blood flow (Iadecola)
- Vascular disease may make clearance of amyloid-β harder; the “glymphatic system” is around blood vessels and helps remove brain waste (Nedergaard)
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
  - Brain changes on MRI or on autopsy
    - Brain infarcts
    - White matter ischemic changes
    - Microbleeds

Associations between vascular risk factors and cognitive decline
Associations between stroke and cognitive decline
Associations between vascular risk factors, brain MRI changes and cognitive decline
Hypertension and Diabetes are Each Associated with Steeper Cognitive Decline

Rawlings et al., Ann Intern Med 2014

Gottesman et al., JAMA Neurology 2014

Worse cognitive performance noted after stroke (REGARDS study)

From Levine et al., JAMA 2015
Blood Pressure and White-Matter Disease Progression in a Biethnic Cohort
Atherosclerosis Risk in Communities (ARIC) Study

Rebecca F. Gottesman, MD, PhD; Josef Coresh, MD, PhD; Diane J. Catellier, DrPH; A. Richey Sharrett, MD, DrPH; Kathryn M. Rose, PhD; Laura H. Coker, PhD; Dean K. Shibata, MD; David S. Knopman, MD; Clifford R. Jack, MD; Thomas H. Mosley, Jr, PhD
(Stroke. 2010;41:3-8.)

Worse cognitive performance is found in people with brain vascular changes

Jokinen et al.,
Cerebrovasc Dis 2009
(LADIS Study)
ApoE and vascular disease: A synergistic effect?

![Graph showing the relationship between ApoE and vascular disease](image)

Rodrigue et al., *JAMA Neurol* 2013

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**Why is the vascular contribution to dementia and AD so important?**

- Vascular disease is preventable
- Vascular disease is very common
- Therefore, this may be a way to prevent AD and other dementia cases
Prevention of vascular disease and AD

<table>
<thead>
<tr>
<th></th>
<th>Prevalence*</th>
<th>PAR (95% CI)</th>
<th>Number of attributable cases in 2010 (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>USA</strong></td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>10.3%</td>
<td>4.5% (2.0-7.3)</td>
<td>240 (107-389)</td>
</tr>
<tr>
<td>Midlife hypertension</td>
<td>14.3%</td>
<td>8.0% (2.2-15.1)</td>
<td>425 (119-798)</td>
</tr>
<tr>
<td>Midlife obesity</td>
<td>13.1%</td>
<td>7.3% (4.3-10.8)</td>
<td>386 (226-570)</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>32.5%</td>
<td>21.0% (5.8-36.6)</td>
<td>1115 (308-1942)</td>
</tr>
<tr>
<td>Depression</td>
<td>19.2%</td>
<td>11.1% (7.5-15.0)</td>
<td>588 (395-796)</td>
</tr>
<tr>
<td>Smoking</td>
<td>20.6%</td>
<td>10.8% (3.0-19.8)</td>
<td>574 (159-1050)</td>
</tr>
<tr>
<td>Low educational attainment</td>
<td>13.3%</td>
<td>7.3% (4.4-10.3)</td>
<td>386 (236-544)</td>
</tr>
<tr>
<td>Combined‡</td>
<td>--</td>
<td>52.7% (25.9-72.8)</td>
<td>2796 (1374-3858)</td>
</tr>
<tr>
<td>Adjusted combined§</td>
<td>--</td>
<td>30.6% (14.5-45.3)</td>
<td>1622 (771-2401)</td>
</tr>
</tbody>
</table>

Combined vascular risk factors account for 9.6 million additional cases of AD worldwide

From Norton et al., Lancet Neurology 2014

Future directions in the study of vascular contributors to Alzheimer’s Disease

- Evaluation of shared genetic risks, or differences in genetic factors that effect an individual’s susceptibility to vascular disease and/or AD
- Study of racial disparities in AD prevalence, which may be partially attributable to differences in vascular disease
- Use of neuroimaging, animal models to further explore mechanism of an additive versus synergistic effect of vascular disease and AD


From Gottesman & Hillis, Lancet Neurology, 2010
Thanks for your attention.