VASCULAR DISEASE AND THE AGEING BRAIN

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Outline

• Dementia results from cumulative burden of several brain pathologies with ageing— including vascular disease

• Evidence during life that cardiovascular disease is closely involved in the development of dementia

• New developments in linking cardiovascular risk factors with the risk of dementia

• Can treatment/prevention of cardiovascular disease or its risk factors reduce the risk of dementia?
Dementia results from cumulative burden of several brain pathologies – including vascular disease
Clinical dementia during life and autopsy findings

**Figure** Distribution of diagnoses in community-dwelling persons with (A) and without (B) dementia

<table>
<thead>
<tr>
<th>PATHOLOGIC DIAGNOSES</th>
<th>PERCENT OF CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or other⁴</td>
<td>0</td>
</tr>
<tr>
<td>AD</td>
<td>20</td>
</tr>
<tr>
<td>Infarction</td>
<td>40</td>
</tr>
<tr>
<td>PD/LBD⁵</td>
<td>60</td>
</tr>
<tr>
<td>Mixed²</td>
<td>80</td>
</tr>
</tbody>
</table>

Dementia
Many roads, but not built in a day

*Neurology® 2007;69:2197-2204*
In most cases, the brains of people dying with dementia show an excess of a mixture of pathologies – neurodegenerative and vascular.

**Brain pathology in dementia**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Dementia</th>
<th>No Dementia</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD pathology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuritic Plaques</td>
<td>85%</td>
<td>57%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Tangles (p-tau)</td>
<td>98%</td>
<td>87%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Vascular pathology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any vascular lesion</td>
<td>81%</td>
<td>76%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>&gt; 1 type of vascular lesion</td>
<td>46%</td>
<td>33%</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Lancet* 2001; 357: 169–75
Mixed AD and vascular pathology more common in groups at high risk for vascular disease.

Figure: Racial differences in mixed pathology.

Pie chart shows proportions of individual and mixed pathologies in black and white decedents with Alzheimer disease (AD) dementia. INF = infarcts; LB = Lewy bodies.
Vascular disease and threshold for dementia

Time

Cognition

Vascular Pathology

Clinical threshold for dementia

high

low

high

low
Evidence during life that cardiovascular disease is closely involved in the development of dementia
Stroke and dementia

1. PREVALENCE OF STROKE BY AGE GROUP: 2009

- Males
- Females

Source: Survey of Disability, Ageing and Carers, 2009

Note: Data for this figure are shown in Table D2.4 in Appendix D.
Sources: Calculations by AIHW using rates based on ADI (2009) and Harvey et al. (2003).

Figure 2.1: Estimated number of people with dementia, by age and sex, 2011

ABS 2009, 2011
Prevalence of dementia before and after stroke

- Between 10-20% of people who suffer a stroke have evidence of dementia before the occurrence of stroke.

- Around 50% of people who have a first-ever stroke experience some cognitive impairment.

- The proportion of people who have evidence of dementia after stroke ranges from ~7% to ~40% depending on several factors.

_Pendlebury et al, Lancet Neurol 2009_
Who is more likely to develop dementia after stroke?

Stroke increases the risk of future dementia by at least two-fold particularly in the setting of recurrent stroke events.

Srikanth et al, Stroke 2006; Withall et al, Aging & Mental Health 2009
Who is more likely to develop dementia after stroke?

*Other known predictors of dementia after stroke include:*

Larger/more severe stroke

Strokes that occur in strategic locations of the brain

Pre-stroke dementia

Greater age & lower educational attainment

Presence of subclinical cerebrovascular disease

*Srikanth et al, Stroke 2006*
“Silent” or “subclinical” cerebrovascular disease

By far more prevalent in older people than clinical strokes
Silent brain infarcts

• Present in 20-30% of older people without dementia

• New silent infarcts hastened cognitive decline and doubled the risk of dementia

Vermeer et al, NEJM, 2003
White Matter Lesions

A large burden of lesions increase the risk of dementia by ~60%

Prins et al, JAMA Neurology, 2004
Cerebral Microbleeds

Presence of microbleeds double the risk of dementia

Akoudad et al, JAMA Neurology 2016
Cerebral microinfarcts

- ~40% of older people have microinfarcts at autopsy
- ~20% have multiple microinfarcts
- Multiple microinfarcts a strong correlate of dementia at death

Pathological Correlates of Dementia in a Longitudinal, Population-Based Sample of Aging

Joshua A. Sonnen, MD,1 Eric B. Larson, MD, MPH,2 Paul K. Crane, MD, MPH,3 Sebastien Haneuse, PhD,2 Ge Li, MD, PhD,4,5 Gerald D. Schellenberg, PhD,3,6 Suzanne Craft, PhD,4,6 James B. Leverenz, MD,5,7,8 and Thomas J. Montine, MD, PhD1

<table>
<thead>
<tr>
<th>Cerebral microinfarcts</th>
<th></th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>1 or 2</td>
<td>1.13</td>
<td>0.40–3.04</td>
</tr>
<tr>
<td>&gt;2</td>
<td>4.80</td>
<td>1.91–10.26</td>
</tr>
</tbody>
</table>

Sonnen et al, Annals Neurol 2007
New developments in linking cardiovascular risk factors with the risk of dementia
Cardiovascular risk factors and dementia

• Mid-life hypertension is an established risk factor for later life dementia – risk greater if untreated

• Mid-life obesity and type 2 diabetes are strong risk factors for late life dementia

• Smoking and high cholesterol are weak risk factors

• Atrial fibrillation is emergingly important as a risk factor

Not all the risk conferred by these factors is explained by the occurrence of stroke.
Type 2 Diabetes and brain atrophy

People with T2D have more brain atrophy than people without T2D irrespective of whether they have strokes on MRI

Mechanisms still unknown

*Moran et al. Diabetes Care, Dec 2013*
Atrial fibrillation

Longer duration of AF conferred a greater risk of future dementia irrespective of the occurrence of clinical stroke

De Bruijn al, Jama Neurology, 2015
Can treatment/prevention of cardiovascular disease or its risk factors reduce the risk of dementia?

Quit Smoking
Exercise Daily
Eat Healthy
To reduce the risk of Heart Disease
What do randomized clinical trials tell us?

- **No direct trial evidence** for primary prevention of dementia or dementia surrogates using vascular therapies (antiplatelet therapy, BP reduction, diabetes therapy, atrial fibrillation therapy)

- **Weak direct trial evidence** for secondary stroke prevention (blood pressure therapy)

Targeting single risk factors may not be as fruitful as adopting a “multifactorial” strategy in current times – where cardiovascular disease is much better treated than before.
Declining incidence of dementia – because of better cardiovascular therapy?

A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II

Fiona E Matthews, Antony Arthur, Linda E Barnes, John Bond, Carol Jagger, Louise Robinson, Carol Brayne, on behalf of the Medical Research Council Cognitive Function and Ageing Collaboration

Figure 1: CFAS I and CFAS II age-specific dementia prevalence

CFAS=Cognitive Function and Ageing Study.

Although many factors could have increased dementia prevalence at specific ages (such as those associated with diabetes, survival after stroke, and vascular incidents), other factors, which could decrease prevalence, such as improved prevention of vascular morbidity and higher levels of education, seem to have had a greater effect. Further work will be done to
Conclusions

• Vascular disease is frequently present in the brains of people with dementia, and is likely to increase the risk of expression of clinical dementia.

• Several cerebrovascular phenotypes (clinical or subclinical) increase the risk of future dementia, and are likely to have a cumulative effect.

• Traditional vascular risk factors increase the risk of dementia, regardless of the risk of stroke that they confer.

• Although single-target clinical trials of vascular risk reduction have not been consistently successful in reducing dementia risk, a multi-target strategy may be more likely to succeed (but is difficult to test).
Conclusions

• Studying what mechanisms (other than stroke) may link important modifiable vascular risk factors with dementia may provide avenues for therapy
  ➢ Diabetes
  ➢ Atrial fibrillation

• Treatment of cardiovascular disease and risk factors is important regardless of the outcome of dementia – and it is possible that these efforts do pay off in the long run for dementia risk reduction
Vascular disease and threshold for dementia
Acknowledgements

• Heart Foundation
• NHMRC
• Alzheimer’s Australia