Cerebrovascular Disease and the Relation of Alzheimer's Disease Pathology to Cognition

David A. Bennett, MD
Rush Alzheimer's Disease Center
Rush University Medical Center, Chicago, IL

Biological Evidence for an Interaction between Alzheimer's and Cerebrovascular Disease
NIA ADC Director’s Meeting
Boston, MA. April 28, 2007
Rush Memory and Aging Project and Religious Orders Study Participants

Rush University Medical Center
Neelum Aggarwal, MD
Zoe Arvanitakis, MD
Lisa Barnes, PhD
Patricia Boyle, PhD
Julia Bienias, ScD
Aron Buchman, MD
Denis Evans, MD
Debra Fleischman, PhD
Jeremiah Kelly, MD
Carlos Mendes de Leon, PhD
Julie Schneider, MD
Raj Shah, MD
Yuxiao Tang, PhD
Robert Wilson, PhD
RADC Staff

University of Pennsylvania
Steven Arnold, MD

University of British Columbia
William Honer, MD

Drexel University
Jonathan Nissanov, PhD

University of California, Davis
Laurel Beckett, PhD

University of California, San Diego
Yan Li, PhD

National Institute on Aging Grants:
P30AG10161; R01AG15819; R01AG17917;
R01AG24480, R01AG24871, K08AG0084;
K23AG23040; K23AG23675
Dad, where do old people come from?
The Religious Orders Study

- > 1,100 older nuns, priests, and brothers without known dementia from across the U.S.
- All agreed to annual cognitive and motor testing
- All agreed to brain donation at the time of death
- > 95% follow-up of survivors
- > 210 persons have developed incident AD
- > 90% autopsy rate with > 375 brain autopsies
Religious Orders Study: Participating Sites
The Rush Memory and Aging Project
… because memories should last a lifetime

• ~ 1,200 residents from about 40 retirement communities and senior housing from across the Chicago area
• All agreed to annual cognitive and motor testing, and blood draw.
• All agreed to donate brain, spinal cord, muscle, and nerve at the time of death
• > 95% follow-up of survivors
• > 135 persons have developed incident AD
• > 80% autopsy rate with > 180 autopsies to date
Baseline Evaluation

Follow-Up Evaluations

F/U 1

F/U 2

F/U X

No Disease

No Cognitive Impairment (No Disease)

Mild Cognitive Impairment

Incident AD

Document Risk Factors

Autopsy

deceased

Autopsy

deceased

Autopsy

deceased

Autopsy

No Pathology

Some Pathology

More Pathology

Objectives:

- AD pathology rarely occurs in isolation
- CVD and AD pathology
  - Primarily additive effects
  - CVD associated with episodic memory and probable AD
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Implications
141 consecutive autopsies (50 with dementia and 91 without dementia)

Age at death = 88; 43% male; 14 years education; mean MMSE = 23

More than 85% had one or more chronic brain abnormalities
  - 57% met NIA-Reagan criteria for AD
  - 37% had cerebral infarctions
  - 17% had PD/LBD

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Brain infarction and the clinical expression of AD. The nun study.

Pathologic correlates of late onset dementia in a multicentre, community based population in England and Wales.

AD lesions and infarcts in demented and non-demented Japanese-American men.

Cognitive impact of subcortical vascular and Alzheimer's disease pathology.
Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology

<table>
<thead>
<tr>
<th>Model, predictors*</th>
<th>Odds of dementia</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. One unit AD pathology†</td>
<td>4.40</td>
<td>2.33–8.32</td>
</tr>
<tr>
<td>2. One unit of AD pathology</td>
<td>4.62</td>
<td>2.41–8.83</td>
</tr>
<tr>
<td>Presence of macroscopic infarctions</td>
<td>2.80</td>
<td>1.26–6.21</td>
</tr>
</tbody>
</table>

Religious Orders Study
Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology


Religious Orders Study
Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology

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<tr>
<th>Models*</th>
<th>Episodic memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. One unit of AD pathology</td>
<td>−0.96 (&lt;0.0001)</td>
</tr>
<tr>
<td>2. One unit of AD pathology</td>
<td>−0.99 (&lt;0.0001)</td>
</tr>
<tr>
<td>Presence of macroscopic infarctions</td>
<td>−0.48 (0.02)</td>
</tr>
</tbody>
</table>

## Subcortical Infarcts, Alzheimer’s Disease Pathology, and Memory Function in Older Persons

<table>
<thead>
<tr>
<th>Model</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD pathology(^b)</td>
<td>9.02 (3.86–21.13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cerebral infarcts</td>
<td>5.06 (1.98–12.92)</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 2(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD pathology(^b)</td>
<td>8.76 (3.80–20.19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Subcortical infarcts</td>
<td>3.93 (1.47–10.49)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

# Subcortical Infarcts, Alzheimer’s Disease Pathology, and Memory Function in Older Persons

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<tr>
<th>Model</th>
<th>Episodic Memory</th>
<th>$p$</th>
</tr>
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<tbody>
<tr>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD pathology&lt;sup&gt;b&lt;/sup&gt;</td>
<td>$-1.00$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Cerebral infarcts</td>
<td>$-0.48$</td>
<td>$0.005$</td>
</tr>
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<td>Model 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
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<td>$0.0001$</td>
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<td>Subcortical Infarcts</td>
<td>$-0.48$</td>
<td>$0.01$</td>
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## Mixed Brain Pathologies Account for Most Dementia Cases in Community-Dwelling Older Persons

<table>
<thead>
<tr>
<th>Pathologic Diagnosis</th>
<th>No dementia</th>
<th>Probable AD</th>
<th>Possible AD</th>
<th>Other dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>“pure” AD</td>
<td>22</td>
<td>13</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>AD + infarction</td>
<td>6</td>
<td>17</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>AD + PD/LBD</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>AD + infarction + PD/LBD</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AD + other</td>
<td>2(^1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No chronic abnormalities</td>
<td>26</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infarctions</td>
<td>16</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>PD/LBD</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infarctions + PD/LBD</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>4(^2)</td>
<td>0</td>
<td>0</td>
<td>1(^3)</td>
</tr>
</tbody>
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Memory and Aging Project
AD pathology rarely occurs in isolation
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Implications

Objectives:
Apolipoprotein E ε4 allele, AD pathology, and the clinical expression of Alzheimer’s disease

<table>
<thead>
<tr>
<th>Pathologic indices</th>
<th>Terms</th>
<th>Model 1 Odds (95% CI)</th>
<th>Model 2 Odds (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global pathology</td>
<td>ε4 allele</td>
<td>3.46 (1.44–8.33)</td>
<td>1.58 (0.56–4.43)</td>
</tr>
<tr>
<td>Pathology</td>
<td>—</td>
<td>—</td>
<td>6.02 (2.59–13.98)</td>
</tr>
</tbody>
</table>


Religious Orders Study
The Apolipoprotein E ε4 Allele Increases the Odds of Chronic Cerebral Infarction Detected at Autopsy in Older Persons

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Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function


Religious Orders Study
Diabetes is related to cerebral infarction but not to AD pathology in older persons

Diabetes is related to cerebral infarction but not to AD pathology in older persons

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<tr>
<th>Pathologic marker</th>
<th>OR</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Cerebral infarction</td>
<td>2.47</td>
<td>1.16, 5.24</td>
</tr>
<tr>
<td>Cortical infarction</td>
<td>3.30</td>
<td>1.13, 9.63</td>
</tr>
<tr>
<td>Subcortical infarction</td>
<td>3.14</td>
<td>1.44, 6.83</td>
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Chronic Psychological Distress and Risk of Alzheimer’s Disease in Old Age

Outcome measure | Model term                                      | Est. slope (SE); p value | Est. slope (SE); p value | Est. slope (SE); p value |
-----------------|------------------------------------------------|--------------------------|--------------------------|--------------------------|
Global cognition | distress proneness                              | -0.037 (0.015); 0.021   | -0.037 (0.017); 0.039   | -0.037 (0.017); 0.039   |
                 | global pathology                                | -0.481 (0.212); 0.029   | -0.061 (0.014); <0.001   | -0.036 (0.031); 0.263   |
                 | tau tangles                                      |                          |                          |                          |
                 | amyloid load                                     |                          |                          |                          |
Episodic memory  | distress proneness                              | -0.042 (0.019); 0.028   | -0.046 (0.015); 0.005    | -0.050 (0.019); 0.013   |
                 | global pathology                                | -0.755 (0.224); 0.002   | -0.081 (0.014); <0.001   |                          |
                 | tau tangles                                      |                          |                          |                          |
                 | amyloid load                                     |                          |                          |                          |

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Non-Cognitive Manifestations of AD Pathology

Parkinsonian-like signs and risk of incident Alzheimer’s disease in older persons.

Neurofibrillary tangles in the substantia nigra are related to gait impairment in older persons.

Change in body mass index (BMI) and risk of incident Alzheimer’s disease (AD).

Body mass index in older persons is associated with Alzheimer’s disease pathology.

Olfactory identification and incidence of mild cognitive impairment in old age.

The relation of cerebral AD pathology to odor identification in old age.
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AD puzzle (paradigm) over past two decades:

- Derivative of these criteria:
  - Clinical (Probable) AD – progressive dementia with memory loss
  - Pathologic AD – density of plaques and tangles
  - “Definite AD” – clinical phenotype and AD pathology

PRACTICE GUIDELINE

Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease

G McKhann, D Drachman, M Folstein, R Katzman, D Price and EM Stadlan
“Any Alzheimer’s disease changes in the postmortem brain (i.e., diffuse amyloid or neuritic plaques, neurofibrillary tangles) … are considered to be pathological even in instances where they appear to be incidental.”
Recommendation

- Abolish current clinical-pathologic definition of disease
- Define AD neuropathologically
- “AD” may:
  - be clinically silent
  - cause structural changes on neuroimaging
  - cause MCI or dementia
  - cause other clinical manifestations, even in the absence of cognitive impairment
    - parkinsonian signs
    - loss of body mass index
    - loss of odor identification
    - neuropsychiatric features, e.g., depression?
- Public Health burden of “AD” is much larger than currently recognized
Staging Alzheimer’s Disease

- Stage I – asymptomatic “widespread” amyloid deposition with or without tangles

- Stage II – asymptomatic amyloid deposition with tangles and “significant” structural changes on MRI

- Stage III – mild cognitive or motor impairment, or neuropsychiatric features

- Stage IV – dementia, usually with motor impairment and neuropsychiatric features
Dad, where do old people come from?
What it takes to prevent dementia?

- Dedicated researchers
- Study volunteers
- Money
- Time
- Imagination
IMAGINE

(apologies to John Lennon)
Imagine there’s no Alzheimer’s
It’s easy if you try
No plaques or tangles
Old neurons do not die
Imagine all old people
Making new memories

Imagine there’s no VaD
It isn’t hard to do
No strokes or infarcts
No WML’s, too
Imagine all old people
Planning life ahead

Imagine there’s no LBD
I wonder if you can
No protein deposits
α-synuclein
Imagine all old people
Standing, walking tall

You may say I’m a dreamer
But I’m not the only one
I hope someday you’ll join us
And the fight against dementia will be won

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