PATHOLOGIC HETEROGENEITY OF CLINICALLY DEFINED AD

Embracing heterogeneity:
Apprehending an increasingly complex disease in the age of biomarkers

Clinical core Thematic Session /ADC meeting Boston 2017

Julie A. Schneider, M.D. M.S.
The Deborah R. And Edgar D. Jannotta Presidential Professor of Pathology and Neurological Sciences
Associate Director, Rush Alzheimer's Disease Center
Rush University Medical Center
• Older data on mixed pathology
• Pathologies; additive effect/impact
• Updated data with additional pathologies.
• Special considerations
Mixed brain pathologies common in MCI and probable AD

![Diagram showing pathology by clinical status](image)

*Fig. Pathology by clinical status proximate to death. (Blue shades) Pathologic diagnosis of Alzheimer disease (AD). Clockwise: light blue = pathologic diagnosis of AD only; dark blue = pathologic diagnosis of AD and neocortical Lewy bodies (LB); medium blue = pathologic diagnosis of AD and cerebral infarcts (I); aqua = pathologic diagnosis of AD, I, and LB. (Red shades) I and/or LB (with no pathologic diagnosis of AD). Clockwise: pink = I or LB; red = I and LB. (White) No pathologic diagnosis of AD, no I, no LB.*


* Estimates do not include vascular path other than gross infarcts

** Estimates do not include milder amounts of AD pathology
The pathologies of the aging brain

**NEURODEGENERATIVE**
- Alzheimer’s disease
- Lewy body disease
- TDP-43 pathology
- Hippocampal sclerosis

**VASCULAR**
- Macroinfarcts
- Microinfarcts
- CAA
- Atherosclerosis
- Arteriolosclerosis
Figure 1. Probability of dementia by increasing levels of Alzheimer's disease (AD) pathology, showing additive effects of macroscopic infarcts, microinfarcts and neocortical Lewy bodies.

Schneider JA et al. Brain 2012;135:3005-3014
HS - higher odds of dementia and AD dementia

Interaction with TDP such that HS with TDP had higher odds
Figure 2. Odds ratios for clinical Alzheimer’s-type dementia
Odds ratios compared to not having pathologic diagnosis of AD or TDP-43 pathology, from a model adjusted for age, sex, education, cerebral infarcts, Lewy bodies, and Hippocampal sclerosis.

James BD et al., Brain. 2016 Sep 30. pii: aww224. [Epub ahead of print]
Updated data on mixed pathologies

• N= 1078 – deceased autopsied from Religious Orders Study, Rush Memory and Aging Project and Minority Aging Research Study with final diagnosis proximate to death (~7 months) of NCI, MCI, or probable AD

• Age at death, 89 years, SD=6.5;
• 32% men;
• Mean education, 16 years
<table>
<thead>
<tr>
<th>Pathology</th>
<th>Clinical Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Cognitive Impairment (n=360)</td>
</tr>
<tr>
<td>No Vascular or Neurodegenerative</td>
<td>50 (13.89%)</td>
</tr>
<tr>
<td>Vascular only</td>
<td>102 (28.33%)</td>
</tr>
<tr>
<td>Other Degenerative only</td>
<td>14 (3.89%)</td>
</tr>
<tr>
<td>Other Degenerative + Vascular (no AD)</td>
<td>41 (11.39%)</td>
</tr>
<tr>
<td>AD only</td>
<td>30 (8.33%)</td>
</tr>
<tr>
<td>AD + Vascular</td>
<td>75 (20.83%)</td>
</tr>
<tr>
<td>AD + Other Degenerative</td>
<td>6 (1.67%)</td>
</tr>
<tr>
<td>AD + otherDegenerative + Vascular</td>
<td>42 (11.67%)</td>
</tr>
<tr>
<td>Mild Cognitive Impairment (n=271)</td>
<td>12 (4.43%)</td>
</tr>
<tr>
<td>Vascular only</td>
<td>57 (21.03%)</td>
</tr>
<tr>
<td>Other Degenerative only</td>
<td>8 (2.95%)</td>
</tr>
<tr>
<td>Other Degenerative + Vascular (no AD)</td>
<td>28 (10.33%)</td>
</tr>
<tr>
<td>Probable AD (n=447)</td>
<td>4 (0.89%)</td>
</tr>
<tr>
<td>AD only</td>
<td>20 (7.38%)</td>
</tr>
<tr>
<td>AD + Vascular</td>
<td>65 (23.99%)</td>
</tr>
<tr>
<td>AD + OtherDegenerative</td>
<td>17 (6.27%)</td>
</tr>
<tr>
<td>AD + otherDegenerative + Vascular</td>
<td>64 (23.62%)</td>
</tr>
<tr>
<td>Probable AD (n=447)</td>
<td>35 (7.83%)</td>
</tr>
<tr>
<td>AD only</td>
<td>14 (3.13%)</td>
</tr>
<tr>
<td>AD + Vascular</td>
<td>122 (27.29%)</td>
</tr>
<tr>
<td>AD + OtherDegenerative</td>
<td>34 (7.61%)</td>
</tr>
<tr>
<td>Probable AD (n=447)</td>
<td>210 (46.98%)</td>
</tr>
</tbody>
</table>
Figure 1 – Prevalence of Mixed Pathologies in ROS/MAP cohort
Prevalence of mixed pathologies in ROS/MAP subjects with a clinical diagnosis of no cognitive impairment, mild cognitive impairment, and probable Alzheimer’s disease. Key: v – vascular; d – degenerative; dv – degenerative vascular; AD – Alzheimer’s disease; 0 – no vascular or neurodegenerative pathology.
Figure 2 – Prevalence of Mixed AD with Vascular/Neurodegenerative Pathologies in the ROS/MAP cohort.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=804)</th>
<th>Age 65-89 (n=503)</th>
<th>Age 90+ (n = 301)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death, yrs (SD)</td>
<td>87.7 (6.7)</td>
<td>83.8 (4.8)</td>
<td>94.3 (3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia, no. (%)</td>
<td>304 (37.8%)</td>
<td>143 (28.4%)</td>
<td>161 (53.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AD</td>
<td>493 (61.3%)</td>
<td>279 (55.5%)</td>
<td>214 (71.1%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Infarcts</td>
<td>272 (33.8%)</td>
<td>147 (29.2%)</td>
<td>125 (41.5%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Single path</td>
<td>374 (46.5%)</td>
<td>238 (47.3%)</td>
<td>136 (45.2%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Mixed path</td>
<td>225 (28.0%)</td>
<td>113 (22.5%)</td>
<td>112 (37.2%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AD + LB</td>
<td>41 (5.1%)</td>
<td>25 (5.0%)</td>
<td>16 (5.3%)</td>
<td>0.83</td>
</tr>
<tr>
<td>AD + Infarcts</td>
<td>162 (20.2%)</td>
<td>79 (15.7%)</td>
<td>83 (27.6%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Pathology and dementia in the oldest old (age 90+ vs. <90)

James BD et al., JAMA. 2012 May 2;307(17):1798-800.
Other special populations

- Clinic vs. Community...

**Single vs. Mixed Neuropathology (all clinical dementias)**

![Pie charts comparing community and clinic samples for single vs. mixed neuropathology.](Schneider JA et al., J. Alz. Disease 2009)
Does not include atherosclerosis, arteriolosclerosis, CAA, TDP, HS...


Figure 3. Variation in cognitive decline explained by the pathologic indices (grey) and the residual, unexplained variation in cognitive decline (white) derived from fully adjusted models.
Acknowledgments

- **Rush Alzheimer’s Disease Center**
  - Neelum Aggarwal, MD
  - Konstantinos Arfanakis, PhD
  - Zoe Arvanitakis, MD, MS
  - Lisa Barnes, PhD
  - David Bennett, MD
  - Patricia Boyle, PhD
  - Aron Buchman, MD
  - Robert Dawe, PhD
  - Debra Fleischman, PhD
  - Bryan James, PhD
  - Sue Leurgans, PhD
  - Sukriti Nag, MD, PhD
  - Rita Shapiro, DO
  - Raj Shah, MD
  - Lei Yu, PhD
  - Robert Wilson, PhD

- **Rush Alzheimer’s Disease Center Staff**

- **National Institute on Aging**

- **Alzheimer’s Association**

- **Illinois Department Public Health**

- **Elsie Heller Brain Bank Endowment Fund**

- **Robert C. Borwell Endowment Fund**

- **Study Participants**

- **Religious Orders Study**

- **Rush Memory and Aging Project**
“I’m stumped. We’ll have to wait for the autopsy.”