Why is Representative Brain Donation Important for Research on Aging and Dementia?

Julie A. Schneider, M.D.

Breakout Session: The Diversification of Brain Tissue: Why and Ways Forward

Fall ADRC Meeting

October 21, 2022
Alzheimer’s disease

• First thought to be presenile dementia because the brain investigated was that of a person in 50s.

• Until autopsies studies of older persons proved otherwise....

> Nature. 1966 Jan 1;209(5018):109-10. doi: 10.1038/209109a0.

Correlation between scores for dementia and counts of 'senile plaques' in cerebral grey matter of elderly subjects

M Roth, B E Tomlinson, G Blessed

PMID: 5927229   DOI: 10.1038/209109a0
Plaques/Tangles

- Then, plaques/tangles in persons with memory loss/dementia = Alzheimer’s disease ...opened floodgate of research....

- Discovery of Amyloid Beta Protein
- Discovery of Paired Helical Filament Tau
- Amyloid Precursor Protein, alpha, beta, gamma secretase
- Apolipoprotein E, Autosomal Dominant Dx (APP, presenilin)
- Mouse and other models of AD
- Anti – amyloid for in-vivo biomarkers/ treatment
Brain Donation propelled our Understanding of Alzheimer’s Dementia

- Continued enrollment of more older persons in longitudinal studies
- More clinical information
- More well characterized brains
Prob AD more than plaques/tangles...


Kapasi A et al. *Acta Neuropathologica* 2017

+ macroscopic infarcts
+ Lewy bodies

+ microinfarcts
+ arteriolosclerosis
+ amyloid angiopathy
+ atherosclerosis
+ TDP/HS (LATE-NC)
More Brains (no cognitive impairment) propelled us further ...

- About 1/3 of older persons have pathologic AD pathology

- Research pivoted to “RESILIENCE”
  - Genetics, Education
  - Cognitive, Social, physical activities
  - Well-being/purpose in life
  - Diet, Exposome
  - Lesser (OR BETTER) inflammation
  - Better repair mechanisms
  - Compensation via other pathways

Kapasi A et al. Acta Neuropathologica 2017
Who and What We See Changes The Way We Think About Disease

“What is “Alzheimer’s Dementia”

Presenile Dementia
Plaques and tangles in person <65

Senile dementia
Plaques in tangles in person >65

Mixed pathology dementia
Plaques/tangles +

Subclinical Dementia pathology
Plaques/tangles in someone without cognitive impairment
### Brains from the Community vs. Clinic

<table>
<thead>
<tr>
<th>Demographics [mean (SD)] and distribution [number (%)] of pathology in two comm</th>
<th>Religious orders study</th>
<th>Memory and aging project</th>
<th>Clinical cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>386</td>
<td>195</td>
<td>392</td>
</tr>
<tr>
<td>Age at death (yrs)</td>
<td>86.2 (SD = 7.0)</td>
<td>88.0 (SD = 5.7)</td>
<td>78.6 (SD = 10.4)</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>17.9 (SD = 3.6)</td>
<td>14.7 (SD = 3.0)</td>
<td>14.9 (SD = 12.2)</td>
</tr>
<tr>
<td>MMSE</td>
<td>21.0 (SD = 9.1)</td>
<td>21.9 (SD = 8.8)</td>
<td>7.3 (SD = 9.3)</td>
</tr>
<tr>
<td>No cognitive impairment</td>
<td>124 (32.1%)</td>
<td>64 (32.8%)</td>
<td>14 (3.6%)</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>87 (22.5%)</td>
<td>54 (27.7%)</td>
<td>9 (2.3%)</td>
</tr>
<tr>
<td>Probable AD</td>
<td>130 (33.7%)</td>
<td>64 (32.8%)</td>
<td>280 (71.2%)</td>
</tr>
<tr>
<td>Possible AD</td>
<td>33 (8.5%)</td>
<td>9 (4.6%)</td>
<td>46 (11.7%)</td>
</tr>
<tr>
<td>Other dementia</td>
<td>12 (3.1%)</td>
<td>4 (2.0%)</td>
<td>43 (10.9%)</td>
</tr>
<tr>
<td>Infarct (any)</td>
<td>189 (49.0%)</td>
<td>89 (45.6%)</td>
<td>109 (27.8%)</td>
</tr>
<tr>
<td>FTLD or other atypical pathology</td>
<td>1 (0.25%)</td>
<td>2 (1.0%)</td>
<td>36 (9.2%)</td>
</tr>
</tbody>
</table>

*Schneider et al.*

<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>Dementia³, 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>AD³</td>
<td>493 (61.3%)</td>
<td>279 (55.5%)</td>
<td>214 (71.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infarcts⁴</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>
Sex differences in mixed neuropathologies in community-dwelling older adults

Most research in men; what about women? Are their Brains different?

Table 4:

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Sample size</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD + TDP/HS</td>
<td>1553</td>
<td>0.82</td>
<td>0.63, 1.08</td>
<td>0.16</td>
</tr>
<tr>
<td>AD + CVD</td>
<td>1558</td>
<td>0.76</td>
<td>0.60, 0.96</td>
<td>0.02</td>
</tr>
<tr>
<td>AD + LBD</td>
<td>1556</td>
<td>1.09</td>
<td>0.82, 1.44</td>
<td>0.57</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>1556</td>
<td>1.37</td>
<td>1.07, 1.75</td>
<td>0.01</td>
</tr>
<tr>
<td>Pure Lewy Body Disease</td>
<td>1556</td>
<td>1.48</td>
<td>0.99, 2.21</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Footnote: The reference group in the models is female; e.g. Males have a higher risk of Parkinson’s disease pathology
Microinfarcts are common and strongly related to dementia in the oldest-old: The 90+ Study

Amanda M. Liesinger1, Neilli R. Graff-Radford2, Ranjan Duara4, Rickey E. Carter3, Fadi S. Hanna Al-Shalhki1, Shunsuke Koga1, Kelly M. Hinkle1, Sarah K. DiLello1, McKenna F. Johnson1, Adel Aziz2, Nilufer Ertekin-Taner1,2, Owen A. Ross1, Dennis W. Dickson1, Melissa E. Murray1,

RESEARCH ARTICLE

Association of Cognition and Dementia With Neuropathologic Changes of Alzheimer Disease and Other Conditions in the Oldest Old

Thomas J. Mc
Lori R. White,
Neurology® 2

JAMA Network Open

Published online 2020 Jun 11. doi: 10.1001/jamanetworkopen.2020.7559
PMCID: PMC7290421
PMID: 32525547

Association of Neighborhood-Level Disadvantage With Alzheimer Disease Neuropathology

W. Ryan Powell, PhD,1,2 William R. Buckingham, PhD,1,2 Jamie L. Larson, PhD,1,2 Leigha Viles, BS,1,2 Meeganao Yu, PhD,1,2 Shahnar Salam, MD, PhD,4,5 Barbara B. Bendin, PhD,1,6,7 Robert A. Risman, PhD,1,6,10 and Amy J. Kind, MD, PhD1,2,6,7

Frequency of LATE neuropathologic change across the spectrum of Alzheimer’s disease neuropathology: combined data from 13 community-based or population-based autopsy cohorts

Mixed pathology is more likely in black than white decedents with Alzheimer dementia

Lisa L. Barnes, PhD, Sue Leurgans, PhD, Neelum T. Aggarwal, MD, Raj C. Shah, MD, Zoe Arvanitakis, MD, Bryan D. James, PhD, Aron S. Buchman, MD, David A. Bennett, MD, and Julie A. Schneider, MD
The neuropathology of Alzheimer disease in African American and white individuals

Consuelo H Wilkins, Elizabeth A Grant, Sarah E Schmitt, Daniel W McKeel, John C Morris

Neuropathological Diagnoses of Demented Hispanic, Black, and Non–Hispanic White Decedents Seen at an Alzheimer's Disease Center

Teresa Jenica Flichtstein, Brittany N Dugger, Lee-Way Lim, John M Olchowy, Sarah T Fornas, Luis Cano-Ramirez, Paul Lott, Dan Mungas, Bruce Reed, Laurel A Bedell, Charles DeCarli

The prevalence of the neuropathological lesions of Alzheimer's disease is independent of race and gender

G Sandberg, W Stewart, J Smialek, J C Troncoso

Neuropathology Studies of Dementia in US Persons other than Non–Hispanic Whites

My-Ie Nguyen, Emily Z Hue, Rachel A Whitmer, Kristen M George, Brittany N Dugger
Diversity within Diversity

• Just like not all white people are alike

• Not all Black, Latino, Asian people are alike
  – Clinic vs. community; old vs. oldest old, male vs. female
  – Socioeconomic Status, Environment, Medical illness, etc., etc.

• Within race studies
The weirdest people in the world?

Joseph Henrich
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They found that people from Western, educated, industrialized, rich and democratic (WEIRD) societies — who represent as much as 80 percent of study participants, but only 12 percent of the world’s population — are not only unrepresentative of humans as a species, but on many measures they’re outliers. May 1, 2010
If most clinical research participation is WEIRD, and donation of Brains is even rarer..., then BRAIN RESEARCH IS WEIRDERER

...and who we study propels diagnosis/medical/basic research/treatment/public health...
THANK YOU!