Hippocampal sclerosis of aging (HS-Aging)

Pete Nelson
HS-Aging literature: Part of fast expanding research derived from ADC and related series

Better data ➔ better conclusions
ADCs and related series: *a new standard*

- Longitudinal assessment
- Improving clinical & neurocognitive evaluation
- More variables, more quantitative correlation

...linked to a key asset: neuropathologic data
NACC data:

**Pitfalls:**

- Dementia clinics have strong bias in recruitment:
  
  **MORE** AD, FTLD, “zebras”
  
  **LESS** Vascular disease, “normals”

-(yes, there are some other potential pitfalls)
NACC data:

Opportunities:

- Increasingly well-audited, high-quality data
- Detailed clinical and pathologic data
- Very large number of cases and controls
- If desired, more recent = better
- Sampling multiple centers is a strength
- A great resource to track correlations and diagnostic trends at state-of-the-art U.S. research centers
HS-Aging

• What is it?
  Neuropathology

• Clinical impact

• Public health impact

• Border zone issues

• New stuff
Diagnosis and definition rest completely on neuropathology
Diagnosis and definition rest completely on neuropathology:

“Hippocampal sclerosis (HS) is defined by pyramidal cell loss and gliosis in CA1 and subiculum of the hippocampal formation that is out of proportion to AD neuropathologic change in the same structures.”
Hippocampal Sclerosis

• Autopsy diagnosis required
• No clinical biomarker
• Aberrant TDP-43 usually
  (Neumann et al, 2006)
  (Amador-Ortiz et al, 2007)
Hippocampal Sclerosis – Neuropathology

• Rapidly changing field

• Laterality

• “Whole brain disease”

• (New stuff later)
Proportion of Hippocampal Sclerosis pathological diagnoses (primary and contributing) among autopsied participants in the NACC Neuropathology Data Set, by year of death, 1990-2012 (N=9,187).
Laterality – 40-50% of cases

HS-ipsilateral

HS-contralateral

Anti-phosphoTDP-43
Laterality – 40-50% of cases

HS-ipsilateral

HS-contralateral

HS-contralateral
Anti-phosphoTDP-43
Laterality – 40-50% of cases

HS-ipsilateral

HS-contralateral

Whole brain disease

HS-contralateral

Anti-phosphoTDP-43
HS-Aging (N=106): Laterality

- Bilateral: 60%
- Unilateral-Left: 25%
- Unilateral-Right: 15%

Nelson PT et al, Brain, 2011
Bilateral 60%

Unilateral - Left 25%

Unilateral - Right 15%

Unilateral sampling → ~20% false negative

HS-Aging (N=106): Laterality

Nelson PT et al, Brain, 2011
HS-Aging
- What is it?
  - Neuropathology
- Clinical impact
- Public health impact
- Border zone issues
- New stuff
Multiple variable regression model:
Testing the impact of many different potential causes of global cognitive impairment (most cases with multiple comorbid pathologies)
Hippocampal sclerosis, either bilateral or unilateral on H&E, was associated with additional global cognitive impairment.
Hippocampal sclerosis, either bilateral or unilateral on H&E, was associated with additional global cognitive impairment
Independent of all other known factors, hippocampal TDP-43 pathology was associated with additional global cognitive impairment.
What about particular cognitive domains?
Cognitive decline in groups stratified by eventual pathology:

Non-linear mixed model trajectory of cognitive scores tracking backward from final cognitive evaluation (mean 8.2 evaluations/patient):

- **A**: Word List Delay
  - Red: No AD, yes HS
  - Blue: Yes AD, no HS
  - Green: Yes AD, yes HS
  - Black: No AD, no HS

- **B**: Verbal Fluency

- **C**: MMSE

- **N=118**
- **Avg 8.2 evals**

*Brain, 2011*
Neurocognitive profile: NACC

Brenowitz et al, JAD, In Press—

Group level differences: HS-Aging, AD, FTLD
Bottom line:

HS-Aging pathology is associated with appreciable added cognitive impairment including in cases with multiple comorbidities
HS-Aging

- What is it?
  Neuropathology
- Clinical impact
- *Public health impact*
- Border zone issues
- New stuff
Hippocampal sclerosis in advanced age: clinical and pathological features

Peter T. Nelson,1,2 Frederick A. Schmitt,2,3 Yushun Lin,4 Erin L. Abner,2 Gregory A. Jicha,2,3 Ela Patel,2 Paula C. Thomason,2 Janna H. Neltner,1 Charles D. Smith,2,3 Karen S. Santacruz,5 Joshua A. Sonnen,6 Leonard W. Poon,7 Marla Gearing,8 Robert C. Green,9 John L. Woodard,10 Linda J. Van Eldik2,11 and Richard J. Kryscio2,4

106 autopsy-confirmed HS-Aging cases
1,004 controls (all with autopsy data)
106 autopsy-confirmed HS-Aging cases
1,004 controls (all with autopsy data)

Acknowledgements
Dr William R. Markesbery performed the neuropathological evaluations for the great majority of cases and controls before his death in January 2010.
In extreme old age, AD pathology becomes LESS prevalent.

Hippocampal sclerosis pathology becomes MORE prevalent.

*Brain, 2011*
Trends by age at death for pathological diagnoses in individuals with dementia. (N=1,061).

Brenowitz et al, JAD, In Press
Pathology by age at death:
Nun Study (N=526); med age >90y.o.

(“Epi- cohort”!!!)
Consensus Recommendations on Pathologic Changes in the Hippocampus: A Postmortem Multicenter Inter-Rater Study

Tuomas Rauramaa, MD, Maria Pikkarainen, PhD, Elisabet Englund, MD, PhD, Paul G. Ince, MD, FRCPath, Kurt Jellinger, MD, PhD, Anders Paetau, MD, PhD, and Irina Alafuzoff, MD, PhD

### TABLE 2. Cases Studied

<table>
<thead>
<tr>
<th>Type Given by the Coordinating Group*</th>
<th>n (male/female)</th>
<th>Mean Age ± SE, years</th>
<th>Clinical Manifestations, %</th>
<th>Brain Weight, Mean ± SE, g</th>
<th>Rapidity of Death as Defined by Johnston et al, %</th>
<th>Postmortem Delay, Mean ± SE, hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lesions</td>
<td>9/6</td>
<td>77 ± 3</td>
<td>10</td>
<td>1,318 ± 77</td>
<td>33, 44, 22</td>
<td>94 ± 10</td>
</tr>
<tr>
<td>+</td>
<td>9/4</td>
<td>69 ± 6</td>
<td>3/6, 33</td>
<td>1,299 ± 57</td>
<td>33, 44, 11, 11</td>
<td>57 ± 11</td>
</tr>
<tr>
<td>1</td>
<td>143/55</td>
<td>77 ± 1</td>
<td>67/76, 26</td>
<td>1,343 ± 12</td>
<td>27, 10, 54, 6</td>
<td>67 ± 4</td>
</tr>
<tr>
<td>2</td>
<td>13/5</td>
<td>76 ± 3</td>
<td>7/6, 31</td>
<td>1,329 ± 59</td>
<td>38, 38, 8, 8</td>
<td>74 ± 11</td>
</tr>
<tr>
<td>3</td>
<td>59/23</td>
<td>77 ± 1</td>
<td>18/41, 71</td>
<td>1,260 ± 24</td>
<td>29, 7, 61</td>
<td>72 ± 8</td>
</tr>
<tr>
<td>4</td>
<td>27/10</td>
<td>78 ± 4</td>
<td>10/17, 74</td>
<td>1,137 ± 51</td>
<td>22, 7, 67</td>
<td>48 ± 11</td>
</tr>
<tr>
<td>Σ</td>
<td>260/77, 107/153</td>
<td>107/153</td>
<td>42, 7</td>
<td>1,300 ± 12</td>
<td>27, 11, 54, 4, 69</td>
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*Type of lesion as described in Materials and Methods and Figure 2: Type +, recent diffuse hypoxic/ischemic degeneration of CA1 Ammon's (CA) neurons; Type 1, small focal infarct (single or multiple); Type 2, extensive infarction of CA1; Type 3, patchy diffuse neuronal degeneration in CA1 sectors associated with or without neuronal lesions of neurodegenerative origin; Type 4, complete neuronal loss from CA1 caused by neurodegeneration, most frequently associated with neurofibrillary tangle formation but sometimes without degenerative pathology.

Johnston et al (17).

Cl, cognitive impairment; NA, not available.
Consensus Recommendations on Pathologic Changes in the Hippocampus: A Postmortem Multicenter Inter-Rater Study

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HS-Aging
HS-Aging
In advanced old age, non-AD diseases underlie much of clinical dementia.

“Classic” clin-path studies addressed much younger cohorts.

Nelson et al
Acta Neuropathologica, 2011
United States Age Groups: Projected % Growth 2000-2020

Source: U.S. Census Bureau
Acta Neuropathologica, 2011
Hippocampal MRI structural changes as an AD biomarker
A large proportion of MRI-visualized hippocampal atrophy is NOT AD!
Just because you can predict future cognitive impairment does not mean you identified its cause, a.k.a. disease (directly relevant to clinical trials)
HS-Aging

• What is it?
  Neuropathology
• Clinical impact
• Public health impact
• Border zone issues
• New stuff
NACC: Subject characteristics at last visit by Hippocampal Sclerosis of aging and Alzheimer’s disease neuropathology (N=1,422)

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<th>Primary Clinical Diagnosis</th>
<th>Probable AD</th>
<th>Possible AD</th>
<th>Normal</th>
<th>Other</th>
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</table>
Subject characteristics at last visit by Hippocampal Sclerosis of aging and Alzheimer’s disease neuropathology (N=1,422)

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<tr>
<th>Primary Clinical Diagnosis</th>
<th>No HS-Aging Pathology</th>
<th>AD Neuropathology positively identified</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No AD-NP (n=675)</td>
<td>AD-NP (n=629)</td>
</tr>
<tr>
<td>Probable AD</td>
<td>209 (31.0)</td>
<td>471 (74.9)</td>
</tr>
<tr>
<td>Possible AD</td>
<td>75 (11.1)</td>
<td>59 (9.4)</td>
</tr>
<tr>
<td>Normal</td>
<td>204 (30.2)</td>
<td>8 (1.3)</td>
</tr>
<tr>
<td>Other</td>
<td>187 (27.7)</td>
<td>91 (14.5)</td>
</tr>
</tbody>
</table>

Mean (SD)

When no HS path present, AD-NP predicted correctly ~85% of the time.
Subject characteristics at last visit by Hippocampal Sclerosis of aging and Alzheimer’s disease neuropathology (N=1,422)

NO AD Neuropathology positively identified 83% of the time
What about the association between HS-Aging pathology and Alzheimer’s disease pathology (plaques and tangles)?
There is **NO** association between APOE genotype and HS-Aging risk

Brenowitz W et al, *JAD*, In Press
Testing the association between HS-Aging pathology and Alzheimer’s disease pathology (plaques and tangles)
No fancy statistical models !!!
Pathology by age at death: Nun Study (N=526); med age >90 y.o.
<table>
<thead>
<tr>
<th>CERAD Neuritic amyloid plaque densities</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sparse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

All participants (n=1,422)
Braak Stage (Neurofibrillary tangles)

More severe AD pathology
Pathologically confirmed **HS pathology**
N=1,455 cases (NACC dataset)

% of cases with cortical HS pathology, by Braak and CERAD stages

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<tr>
<th>CERAD Neuritic amyloid plaque densities</th>
<th>Braak Stage (Neurofibrillary tangles)</th>
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<tbody>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>9.5</td>
</tr>
<tr>
<td>Sparse</td>
<td>14.3</td>
</tr>
<tr>
<td>Moderate</td>
<td>14.3</td>
</tr>
<tr>
<td>Severe</td>
<td>7.1</td>
</tr>
</tbody>
</table>

More severe AD pathology

Brenowitz et al, *JAD*, *In Press*
Both HS-Aging and AD pathology are very prevalent, and frequently co-occur. However, in old patients with minimal AD pathology one frequently sees HS-Aging pathology.
Bad Actor

Bad Situation
Bad Actor \rightarrow \text{Bad Reaction} \\
\downarrow \\
Bad Situation
Amyloid Plaques

Bad Situation
Amyloid Plaques → Bad Situation → Neocortical Tangles
Amyloid Plaques → Neocortical Tangles → Bad Situation → Severe Impairment
Credible—we now know lots of other stimuli/diseases
We now know lots of other diseases including C.T.E.
FTLD Genes → Bad Situation → TDP-43 pathology → Severe Impairment
We now know

Cockayne disease
LRRK2 PD
SNCA PD
FAD
Perry Syndrome
Machado-Joseph disease
NBIA-1

TDP-43 pathology

Impairment
We now know Cockayne disease, LRRK2 PD, SNCA PD, FAD, Perry Syndrome, Machado-Joseph disease, NBIA-1, Chronic traumatic encephalopathy, and TDP-43 pathology.
Age, symptoms, & neuroanatomy: HS-Aging differs **appreciably** from FTLD

Table 3  Comparison of mean age at death and percentage hippocampal sclerosis positive, frontotemporal dementia positive, progressive non-fluent aphasia positive, and semantic dementia positive, between the current case series (bold) and prior case series with frontotemporal lobar dementia with aberrant TDP-43 (FTLD-TDP).

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean death age in years (SD)</th>
<th>Hippocampal sclerosis pathology (%)</th>
<th>FTD or PNFA clinically (%)</th>
<th>Semantic dementia clinically (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS-Ageing (all)</td>
<td>106</td>
<td>92 (7)</td>
<td>100 b</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HS-Ageing–TDP a</td>
<td>71</td>
<td>94 (7)</td>
<td>100 b</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Rohrer et al. (2010)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTLD–TDP type 1 c</td>
<td>9</td>
<td>59 (8)</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>FTLD–TDP type 2 c</td>
<td>5</td>
<td>59 (11)</td>
<td>20</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>FTLD–TDP type 3 c</td>
<td>10</td>
<td>57 (8)</td>
<td>80</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Josephs et al. (2009)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTLD–TDP type 1 d</td>
<td>24</td>
<td>76 (10)</td>
<td>75</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>FTLD–TDP type 2 d</td>
<td>9</td>
<td>74 (10)</td>
<td>56</td>
<td>29</td>
<td>71</td>
</tr>
<tr>
<td>FTLD–TDP type 3 d</td>
<td>6</td>
<td>70 (8)</td>
<td>67</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td><strong>Mackenzie et al. (2006)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTLD–TDP type 1 d</td>
<td>15</td>
<td>69 (5)</td>
<td>93</td>
<td>93</td>
<td>7</td>
</tr>
<tr>
<td>FTLD–TDP type 2 d</td>
<td>9</td>
<td>70 (4)</td>
<td>67</td>
<td>22</td>
<td>77</td>
</tr>
<tr>
<td>FTLD–TDP type 3 d</td>
<td>13</td>
<td>59 (11)</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td><strong>Armstrong et al. (2009)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTLD–TDP sporadic</td>
<td>52</td>
<td>71 (11)</td>
<td>6</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>FTLD–TDP not sporadic</td>
<td>42</td>
<td>70 (9)</td>
<td>7</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>
However, common biochemical pathways and genetic factors are involved
HS-Aging

- What is it?
  Neuropathology
- Clinical impact
- Public health impact
- Border zone issues
- New stuff
Hippocampal sclerosis: a common pathological feature of dementia in very old (≥80 years of age) humans

of people of 80 years of age or older, HpScl was detected in 13 cases (16%), including 9 women and 4 men. The latter group is the subject of this report. The average age for the 13 cases with HpScl (89.2±4.1

Cerebrovascular disease was detected in all 13 cases with HpScl. Microvascular pathology was prominent in all cases and took the form of arteriosclerosis (12 cases) or amyloid angiopathy (6 cases) or both (5 cases).
According to Wikipedia (and Dorland’s Medical Dictionary)—

“The following terms are similar, yet distinct, in both spelling and meaning...Arteriosclerosis is a general term describing any hardening (and loss of elasticity) of medium or large arteries (from the Greek arteria, meaning artery, and sclerosis, meaning hardening); arteriolosclerosis is any hardening (and loss of elasticity) of arterioles (small arteries).”
<table>
<thead>
<tr>
<th>Summary</th>
<th>UK-ADC</th>
<th>Nun Study</th>
<th>NACC</th>
</tr>
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<tbody>
<tr>
<td>Total cases included, N</td>
<td>327</td>
<td>247</td>
<td>1444</td>
</tr>
<tr>
<td>With HS-Aging pathology, N</td>
<td>39</td>
<td>30</td>
<td>157</td>
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<tr>
<td>Age at death (years), mean ± SD</td>
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</tr>
<tr>
<td>No HS-Aging</td>
<td>87.8 ± 5.1</td>
<td>89.9 ± 4.6</td>
<td>88.2 ± 5.7</td>
</tr>
<tr>
<td>% HS-Aging (no AD)</td>
<td>4.6</td>
<td>6.5</td>
<td>4.2</td>
</tr>
<tr>
<td>% AD (no HS)</td>
<td>45.3</td>
<td>19.8</td>
<td>41.9</td>
</tr>
<tr>
<td>% HS-Aging + AD</td>
<td>7.3</td>
<td>5.7</td>
<td>6.4</td>
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We tested presence/severity of multiple parameters for correlation with HS-Aging pathology
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<td>88.0 ± 5.1</td>
<td>90.3 ± 4.8</td>
<td>88.3 ± 5.7</td>
</tr>
<tr>
<td>HS-Aging</td>
<td>90.2 ± 4.6</td>
<td>92.9 ± 5.1</td>
<td>89.1 ± 5.6</td>
</tr>
<tr>
<td>No HS-Aging</td>
<td>87.8 ± 5.1</td>
<td>89.9 ± 4.6</td>
<td>88.2 ± 5.7</td>
</tr>
<tr>
<td>% HS-Aging (no AD)</td>
<td>4.6</td>
<td>6.5</td>
<td>4.2</td>
</tr>
<tr>
<td>% AD (no HS)</td>
<td>45.3</td>
<td>19.8</td>
<td>41.9</td>
</tr>
<tr>
<td>% HS-Aging + AD</td>
<td>7.3</td>
<td>5.7</td>
<td>6.4</td>
</tr>
</tbody>
</table>

Arteriolosclerosis severity correlated with HS-Aging pathology in all 3 datasets
None of these (presence or severity) correlated with HS-Aging pathology:

- Total infarcts
- Micro-infarcts
- Pale infarcts
- Lacunar infarcts
- Hemorrhagic infarcts
- Hemorrhages
- Macro-infarcts
- Cortical Laminar Necrosis
- Atherosclerosis (Circle of Willis)
- Amyloid Angiopathy

Neltner et al, *Brain, In Press*
HS-Aging pathology correlated with presence of regional arteriolosclerosis in age-matched UK-ADC participants

(P value determined by logistic regression controlling for age at death via covariate adjustment; the Bonferroni-Holm method was used to correct for multiple comparisons.)
<table>
<thead>
<tr>
<th>Area</th>
<th>p</th>
<th>Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal cortex (BA 9)</td>
<td>0.0001</td>
<td>Y</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>0.0018</td>
<td>Y</td>
</tr>
<tr>
<td>Posterior Cingulate</td>
<td>0.0014</td>
<td>Y</td>
</tr>
<tr>
<td>Anterior Cingulate</td>
<td>0.0016</td>
<td>Y</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.0023</td>
<td>Y</td>
</tr>
<tr>
<td>Caudate</td>
<td>&lt;0.0001</td>
<td>Y</td>
</tr>
<tr>
<td>Putamen</td>
<td>&lt;0.0001</td>
<td>Y</td>
</tr>
<tr>
<td>Insular cortex (BA13 )</td>
<td>0.0005</td>
<td>Y</td>
</tr>
<tr>
<td>Globus Pallidus</td>
<td>&lt;0.0001</td>
<td>Y</td>
</tr>
<tr>
<td>Temporal cortex (BA 21/22)</td>
<td>0.0032</td>
<td>N</td>
</tr>
<tr>
<td>Parietal cortex (BA 39/40)</td>
<td>0.022</td>
<td>N</td>
</tr>
<tr>
<td>Internal Capsule</td>
<td>0.0767</td>
<td>N</td>
</tr>
</tbody>
</table>
According to Wikipedia (and Dorland’s Medical Dictionary)—

“The following terms are similar, yet distinct, in both spelling and meaning...Arteriosclerosis is a general term describing any hardening (and loss of elasticity) of medium or large arteries (from the Greek arteria, meaning artery, and sclerosis, meaning hardening); arteriolosclerosis is any hardening (and loss of elasticity) of arterioles (small arteries).”
We sought a method that was more rigorous than semiquantitative scoring.
Digital pathology: Relatively unbiased high-throughput morphometry

Neltner et al, *Brain, In Press*
Neltner et al,
Brain, In Press

Frontal Cortex (Brodmann Area 9)
Immunohistochemistry and digital pathology

- SMA
- CD 34
- CD 31
- Collagen IV
- Factor VIII

- Highlights arteriolar walls
- Highlights endothelial lining of all vessels (including capillaries)
- Highlights all vessels (including capillaries)
- No/minimal background staining
- Mild-moderate background staining or lability to fixation
- High background staining

Robust immunohistochemistry after extended formalin fixation
- NOT Selected for digital analysis

Selected for digital analysis
We applied digital pathologic (Aperio ScanScope) methods on a convenience subsample of frontal cortex sections from HS-Aging (N=15) and control (N=42) cases.
We applied digital pathologic (Aperio ScanScope) methods on a convenience subsample of frontal cortex sections from HS-Aging (N=15) and control (N=42) cases. 43,834 α-SMA-positive vascular profiles and 603,798 CD34-positive vascular profiles were evaluated.
Frontal cortex, Brodmann Area 9
Thickened walls and wider vascular profile of SMA+ arterioles in frontal cortex of brains with HS-Aging
Neltner et al,
*Brain, In Press*
Conclusions

HS-Aging:

Distinct “whole brain” disease entity

- High prevalence
- High morbidity
- Neuropathology
  - HS in “oldest-old”
  - TDP-43 pathology
  - Arteriosclerotic
NACC COLLABORATORS:

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Sarah E. Monsell, MS\textsuperscript{1},
Walter A. Kukull, PhD\textsuperscript{1,2}

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NIH/NINDS  K08 Grant
NIH/NINDS  R01 Grants
NIH/NIA  R21 Grants

NIH/NIA  ADC NP Core

NIH/NIA  NACC (U01 AG016976)
Thickening and widening of arterioles in frontal cortex of brains with HS-Aging