DWI Abnormalities in Cerebral Amyloid Angiopathy: A Unique Vasculopathy?

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Disclosures

• Grant funding from governments and foundations: NIH, CIHR, CSN, HSFC, AIHS, C5R.
CONCEPTS

• Small infarction—unrecognized but frequent.
• Frequent silent small infarcts are a feature of cerebral amyloid angiopathy.
• Small concurrent infarcts are seen in other settings too, including small vessel ischemic stroke as well as ICH.
• Even smaller infarcts—microinfarcts— are more numerous but can only be seen pathologically.
59 year woman who underwent MRI for work up of presumed cerebral small vessel disease.
SMALL INFARCTS IN ICH

HYPOTHESIS

Some of the small DWI positive lesions seen in ICH are infarcts caused by small vessel disease.
CEREBRAL AMYLOID ANGIOPATHY (CAA)

- Caused by beta-amyloid deposition in small arteries in leptomeninges and cortex.
- Causes 50-60% of lobar intracerebral hemorrhages.
- Higher risk of recurrence than hypertensive hemorrhages (5-10% per year).
- Often associated with lobar microbleeds, usually 1-4 but sometimes hundreds.

Affects lobar arteries only

Causes lobar ICH

Asymptomatic lobar microbleeds
CAA CAUSES BRAIN ISCHEMIA, TOO

• Small infarcts and microinfarcts seen pathologically.
• High burden of periventricular and subcortical white matter lesions on MRI.
• Blood flow regulation is disturbed in CAA.
HIGH WHITE MATTER LESION BURDEN IN CAA

![FLAIR MRI](image)

**Mean WMH (cm³)**

- **CAA, N=45**
- **Framingham, N=489**
- **Austrian SPS, N=329**

P < 0.001

SMALLER CEREBRAL BLOOD FLOW RESPONSES IN CAA

Abeta formation
↓
Aggregation into Beta-Amyloid
↓
Deposition in Vascular Media

Decreased Vascular Integrity
↓
Bleeding
↓
Microbleeds

Symptomatic Intracerebral Hemorrhage

Fibrosis
Chronic Inflammation
Smooth Muscle Toxicity
↓
Decreased Vascular Reactivity
↓
Repeated Episodes of Low Blood Flow
↓
White Matter Lesions

Microinfarcts

Cracking of vascular media with "vessel in vessel" appearance.

Replacement of media with rigid beta-amyloid (brown immunostain).
Incidental DWI + lesions in 12/78 CAA patients scanned in follow-up or as part of research study.

5/78 had 2 lesions, 7/78 had 1 lesion.

DWI + more common in patients with more microbleeds.

Typical CAA patient has estimated 8 new small infarcts per year.

16-19% of patients with acute lacunar stroke have multiple small DWI + lesions.\(^1,2\)

Not all patients with small DWI + lesions have risk factors for cardioembolism.

– Only 2/10,\(^1\) 4/14\(^2\) and 1/10\(^3\) had atrial fibrillation or LV thrombus.

67 year man with dysarthria and left weakness.

# PREVALENCE OF CONCURRENT SMALL DWI POSITIVE LESIONS

<table>
<thead>
<tr>
<th>CAA/Ischemic small vessel disease</th>
<th>Prevalence</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kimerly et al 2009¹</td>
<td>12/78</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Acute lacunar stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ay et al 1999²</td>
<td>10/62</td>
<td>16%</td>
</tr>
<tr>
<td>Wessels et al 2005³</td>
<td>14/73</td>
<td>19%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICH</th>
<th>Study</th>
<th>Prevalence</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Garg et al 2011⁴</td>
<td>39/95</td>
<td>41%</td>
</tr>
<tr>
<td></td>
<td>Gregoire et al 2011⁵</td>
<td>15/114</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>Menon et al 2012⁶</td>
<td>48/138</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>Prabhakaran et al 2010⁷</td>
<td>27/118</td>
<td>27%</td>
</tr>
</tbody>
</table>

MICROINFARCTS: THE INVISIBLE LESIONS

- Seen microscopically but not on gross pathological examination.
- Mean diameter 0.2-1.0 mm.

## PREVALENCE OF MICROINFARCTS

<table>
<thead>
<tr>
<th>Study name</th>
<th>N</th>
<th>Population</th>
<th>Prevalence of Microinfarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>209</td>
<td>Washington State USA, randomly selected members of Group Health Cooperative</td>
<td>97/209 (46.4%)</td>
</tr>
<tr>
<td>BLSA</td>
<td>179</td>
<td>Baltimore, USA community</td>
<td>39/179 (21.8%)</td>
</tr>
<tr>
<td>Bronx Studies</td>
<td>190</td>
<td>Bronx, USA community including nursing homes</td>
<td>30/190 (15.8%)</td>
</tr>
<tr>
<td>CC75C Study</td>
<td>213</td>
<td>Cambridge, UK, community through general practices</td>
<td>103/213 (48.4%)</td>
</tr>
<tr>
<td>HAAS</td>
<td>285</td>
<td>Honolulu, USA Japanese-American men</td>
<td>55/285 (19.3%)</td>
</tr>
<tr>
<td>Religious Orders Study</td>
<td>425</td>
<td>Older Catholic clergy from multiple U.S. centers</td>
<td>129/425 (30.4%)</td>
</tr>
<tr>
<td>Rush Study of Memory and Aging</td>
<td>148</td>
<td>Chicago, USA community mostly from retirement/seniors housing</td>
<td>35/148 (23.6%)</td>
</tr>
</tbody>
</table>

**Pooled**

| 1649                  | all | 488/1649 (29.6%) |

*Smith EE et al, Lancet Neurology in press.*
CHARACTERISTICS ASSOCIATED WITH MICROINFARCTS

- Advanced age.
- Cerebral amyloid angiopathy.
- Arteriolosclerosis.
- Macroscopic—predominantly lacunar—infarcts and microhemorrhages.
  - But, half of patients with microinfarcts do not have macroinfarcts.
MICROINfarcts AND OR (UNADJUSTED) FOR DEMENTIA

Odds Ratio for Dementia in Persons with Microinfarcts

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT⁶</td>
<td>2.96 (1.64, 5.33)</td>
<td>15.47</td>
</tr>
<tr>
<td>BLSA³⁴</td>
<td>10.51 (3.87, 28.51)</td>
<td>10.31</td>
</tr>
<tr>
<td>Bronx Studies²⁴</td>
<td>0.88 (0.38, 2.83)</td>
<td>12.15</td>
</tr>
<tr>
<td>CC75C⁸²</td>
<td>1.50 (0.87, 2.58)</td>
<td>16.12</td>
</tr>
<tr>
<td>HAAS⁹</td>
<td>3.10 (1.68, 5.71)</td>
<td>15.16</td>
</tr>
<tr>
<td>Religious Orders Study¹⁹</td>
<td>1.69 (1.12, 2.57)</td>
<td>17.88</td>
</tr>
<tr>
<td>Rush Study of Memory and Aging¹⁷</td>
<td>1.37 (0.63, 2.99)</td>
<td>12.90</td>
</tr>
<tr>
<td>Overall (I-squared=70.8%, p=0.002)</td>
<td>2.15 (1.38, 3.37)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*NOTE: Weights are from random effects analysis.*

Smith EE et al, Lancet Neurology in press.
## MICROINfarcts: More Important Cause of Dementia Than Macroinfarcts

<table>
<thead>
<tr>
<th>Study name</th>
<th>N</th>
<th>Adjusted Odds Ratio (OR) for Dementia (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>221</td>
<td>Negligible (reference)</td>
<td>In contrast to microinfarcts, macroinfarcts were not significant in univariate analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 or 2 OR 1.13 (0.40-3.04)</td>
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<tr>
<td></td>
<td></td>
<td>High 4.80 (1.91-10.26)</td>
<td></td>
</tr>
<tr>
<td>BLSA</td>
<td>179</td>
<td>9.3 (3.4-25)</td>
<td>Both microinfarcts and macroinfarcts independently associated with dementia.</td>
</tr>
<tr>
<td>Bronx Studies</td>
<td>190</td>
<td>0.6 (0.2-1.9)</td>
<td>Neither microinfarcts nor macroinfarcts were associated with dementia.</td>
</tr>
<tr>
<td>CC75C Study</td>
<td>213</td>
<td>2.2 (1.0-5.1)</td>
<td>In contrast to microinfarcts, macroinfarcts were not significant in univariate analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negligible (reference)</td>
<td></td>
</tr>
<tr>
<td>HAAS</td>
<td>285</td>
<td>Intermediate OR 2.36 (0.87-6.41)</td>
<td>Microinfarcts were independently associated with dementia when controlling for macroinfarcts, but macroinfarcts were not significant.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High 4.59 (2.07-10.19)</td>
<td></td>
</tr>
<tr>
<td>Religious Orders Study</td>
<td>425</td>
<td>1.77 (1.07-2.92)</td>
<td>Both microinfarcts and macroinfarcts independently associated with dementia.</td>
</tr>
<tr>
<td>Rush Study of Memory and Aging</td>
<td>148</td>
<td>0.71 (0.26-1.97)</td>
<td>Controlling for macroinfarcts, microinfarcts were not significant.</td>
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</table>

= microinfarcts independently associated with dementia, after taking macroscopic infarcts into account.

Smith EE et al, Lancet Neurology in press.
CONCLUSIONS SO FAR

• Small infarcts, predominantly “silent” or “covert”, are frequent in cerebral small vessel diseases.
• The larger of the small infarcts can be visualized using neuroimaging.
• Primary ICH is caused by cerebral small vessel disease.
• Some of the small DWI + lesions seen in ICH could represent small infarcts caused by small vessel disease.
WHAT IS THE ROLE OF BLOOD PRESSURE DECREASES?

- Larger BP reductions associated with DWI+ in 3 studies.\(^1,2,3\)
- However, in one study 5/27 patients with small DWI+ lesions did not have MAP decrease >40%.\(^1\)
- New infarcts at 30 days compared to baseline seen in 25/113, after BP has presumably stabilized.\(^2\)
- Associations with microbleeds,\(^2,4\) probable CAA,\(^4\) hypertension,\(^1\) leukoaraiosis,\(^4\) and previous ischemic stroke\(^1\) suggest that severity of cerebral small vessel disease is a risk factor for small DWI+.
- 2-hit hypothesis: cerebral small vessel disease is sufficient to cause small infarcts, but the frequency is greatly increased when cerebral small vessel disease is accompanied by sudden dramatic blood pressure lowering.

NEEDED

- Better ways to visualize small infarcts in vivo, including the currently invisible microinfarctions.
- Pathological studies.
- More information on small infarction and relationship to clinical outcomes.
THANK YOU

ACKNOWLEDGEMENTS:

• MGH Hemorrhagic Stroke Research Group (including Dr. Steven Greenberg and Dr. Taylor Kimberly).
• Dr. Julie Schneider and Chunhui Yang for the pathology slides.
• Dr. Joanna Wardlaw.
• Moderators and AHA for hosting this session.