Sex Differences in Stroke

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Disclosures

• I have no relevant disclosures
Types of Stroke

- Intracranial Hemorrhage: 87%
- Subarachnoid Hemorrhage: 10%
- Ischemic: 3%

Source: AHA Disease Statistics Circulation 2012;125 (e2-e220)
Case

• 85 F with recent loss of her longtime husband.
• She was found by her daughter in the afternoon, who visits weekly and spoke to her the day before.
• Focal?
• Exam shows left sided weakness, face and arm > leg.
• Gaze preference.
• Neglect.
• Where is it?
Case continued

• CTA shows proximal right MCA occlusion at M1 but no significant stenosis in the contralateral carotid, minimal calcifications.

• Likely etiology?

• Time of onset was unknown.

• What would you do?
Acute Imaging
Anything to save?

CBF (<30%) volume: 96.4 ml
Mismatch volume: 130.2 ml
Mismatch ratio: 2.4

Perfusion (Tmax>6.0s) volume: 226.6 ml
Etiology?
Cumulative frequency of stroke etiology in women and men with AIS

Atrial Fibrillation

- Women experience more symptoms from AF
- Less likely to receive rhythm control or catheter ablation
- Poorer quality of life
- Higher risk for stroke and death than men with AF
- Biology vs. Sociology?
- Women are more likely to be living alone or widowed before (and after) a stroke
- Less likely to be anticoagulated compared to age-matched men? “frailty”? 
- Under represented in clinical trials

Figure 3 | Participation of women in anticoagulation trials for stroke prevention in atrial fibrillation. A pie chart showing proportion of women (orange) represented in anticoagulation trials compared with men (blue). The numbers indicate the year of publication of the study. The sizes of the individual pie charts correspond to the relative overall size of the trial.
So how is this woman going to do?

- More likely to be disabled by her stroke
- More likely to die from her stroke
- More likely to end up in a skilled nursing facility
- More likely to have cognitive disability after stroke
- More likely to develop post-stroke depression
- **BUT** also more likely to have functional deficits before her stroke
- **AND** more likely to live alone
Age and other factors matter in outcome

Policy: NIH to balance sex in cell and animal studies

http://orwh.od.nih.gov/research/index.asp
Hypertension and the SPRINT trial

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Intensive Treatment</th>
<th>Standard Treatment</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>243/4678 (5.2)</td>
<td>319/4683 (6.8)</td>
<td>0.75 (0.64–0.89)</td>
<td>0.75 (0.64–0.89)</td>
</tr>
<tr>
<td>Previous CKD</td>
<td></td>
<td></td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>135/3348 (4.0)</td>
<td>193/3367 (5.7)</td>
<td>0.70 (0.56–0.87)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>108/1330 (8.1)</td>
<td>126/1316 (9.6)</td>
<td>0.82 (0.63–1.07)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>&lt;75 yr</td>
<td>142/3361 (4.2)</td>
<td>175/3364 (5.2)</td>
<td>0.80 (0.64–1.00)</td>
<td></td>
</tr>
<tr>
<td>≥75 yr</td>
<td>101/1317 (7.7)</td>
<td>144/1319 (10.9)</td>
<td>0.67 (0.51–0.86)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>77/1684 (4.6)</td>
<td>89/1648 (5.4)</td>
<td>0.84 (0.62–1.14)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>166/2994 (5.5)</td>
<td>230/3035 (7.6)</td>
<td>0.72 (0.59–0.88)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>62/1454 (4.3)</td>
<td>85/1493 (5.7)</td>
<td>0.77 (0.55–1.06)</td>
<td></td>
</tr>
<tr>
<td>Nonblack</td>
<td>181/3224 (5.6)</td>
<td>234/3190 (7.3)</td>
<td>0.74 (0.61–0.90)</td>
<td></td>
</tr>
<tr>
<td>Previous cardiovascular disease</td>
<td></td>
<td></td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>149/3738 (4.0)</td>
<td>208/3746 (5.6)</td>
<td>0.71 (0.57–0.88)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>94/940 (10.0)</td>
<td>111/937 (11.8)</td>
<td>0.83 (0.62–1.09)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>≤132 mm Hg</td>
<td>71/1583 (4.5)</td>
<td>98/1553 (6.3)</td>
<td>0.70 (0.51–0.95)</td>
<td></td>
</tr>
<tr>
<td>&gt;132 to &lt;145 mm Hg</td>
<td>77/1489 (5.2)</td>
<td>106/1549 (6.8)</td>
<td>0.77 (0.57–1.03)</td>
<td></td>
</tr>
<tr>
<td>≥145 mm Hg</td>
<td>95/1606 (5.9)</td>
<td>115/1581 (7.3)</td>
<td>0.83 (0.63–1.09)</td>
<td></td>
</tr>
</tbody>
</table>
Psychosocial Factors

• Depression and psychosocial stress increase risk for incident stroke by 25% to 45% in women

• Higher serum inflammation? Compliance?

  • Social Isolation (loneliness) increases risk of mortality
  • Isolation increases risk of first stroke Isolation leads to poorer recovery (controlled for NIHSS)
  • Stroke patients with low social support have increased risk of recurrent stroke
Epidemic of Loneliness

- 52% of women live alone compared to 29% for men after the age of 80
- May outlive not only spouses/partners but also their friends and children
- Cardiovascular, nervous and immune targets
Biology: The detrimental effects of isolation can be modeled in animals!
Infarct Size was equivalent at 30 and 90 days when isolation occurred three days after stroke (to control for infarct size)
Mortality

![Mortality Graph](image)

- Sham
- SI
- PH-SP
- PH-HP

Significance levels:
- P<0.01
- P<0.05
Translational Failure: Estrogen

Female

OVX Female
Ischemic stroke risk - WHI hormone trial

Hendrix, S. L. et al. Circulation 2006;113:2425-2434
Timing matters!
Case

- 41 yo G5P4 presented with an acute onset of right hemiparesis and aphasia at 9am
- Last seen at 8:30 am, called husband “not feeling well”
- On arrival she was mute, lying on the floor
- In ED she had a NIHSS of 22. Alert, awake, global aphasia, left gaze preference, visual field cut, normal pupils, right facial, 0/5 on right and moving spontaneously on left.
- 5 months pregnant-What next?
- TPA?
Microchimerism and Disease

• Humans...how these cells identified in humans

• “Good Microchimerism” Hypothesis: cure

• “Bad Microchimerism” Hypothesis: cause
Mouse Model: **Fetal** Microchimera

- GFP+/-×GFP-/-
- GFP+/+♂
- GFP+-/-
- GFP+-/-

Induce 90min MCAO 3-4 wks after delivery

Analyze Brain and Blood for GFP+ cells at 72hrs & 30d post-MCAO
GFP+ Fetal Cells are Present in the Maternal Ischemic Brain

Non-Stroke Side

Stroke Side

DAPI

TexRed (autofluorescent)

GFP

MERGE

DAPI

Anti-GFP

GFP

MERGE

20 µm
Homing of Fetal Cells to Ischemic Injury

Fetal Microchimera: 90min, 72hr, 3-4 weeks post-partum

CV stain of adjacent section
30 days after Stroke

Non-Stroke Side

Stroke Side

DAPI

T Lectin

GFP

Non-Stroke Side

Stroke Side

DAPI

T Lectin

GFP

DAPI

T Lectin

GFP

DAPI

T Lectin

GFP

DAPI
Background: Neuroimmunology

- Bi-directional communication between the immune system and the nervous system
- The CNS as an immune privileged site
- Inflammation plays a role in the etiology of a variety of neurological diseases
Systemic Effects of Stroke

• Peripheral Effects
• Role of Peripheral Leukocytes/Myeloid Cells
• Local Response...Microglia/Astrocytes?
• Aging... T cell deficits? Infections?
Hemorrhagic transformation (HT) after experimental stroke in aged mice: Blood marked by arrows-mimics clinical populations
Fat in aged versus young mice
Significantly higher peripheral cells in the aged brain AT BASELINE
High expression of T cell adhesion markers on CD8 T cells in aged in blood and brain compared to young mice
Aged mice have smaller infarcts but much poorer recovery and high mortality.
The Composition of Infiltrating Leukocytes Differs with Age

Young Sham
Young Stroke
Aged Sham
Aged Stroke

Peripheral Leukocytes

Microglia

CD11b

CD45

YOUNG
Monocytic

20% Ly6G⁺ Neutrophils
52% Ly6C⁺ Monocytes
28% Ly6G⁻/Ly6C⁻ Other

AGED
Neutrophilic

48% Ly6G⁺ Neutrophils
37% Ly6C⁺ Monocytes
15% Ly6G⁻/Ly6C⁻ Other
Generating Heterochronic Bone Marrow Chimeras (hBMC)

![Diagram showing the process of generating heterochronic bone marrow chimeras (hBMC).](image)

- **Young → Young**
- **Old → Young**
- **And**
- **Young → Old**
- **Old → Old**

**Immunostaining Images:**
- *Iba1* (left)
- *DAPI* (blue)
- *GFP* (green)
- *Cresyl Violet* (right)
Young bone marrow contributes to enhanced recovery in aged mice
Aged bone marrow contributes to poorer recovery in young mice
Aged bone marrow increased hemorrhagic transformation in young mice and young BMT reversed this in aged mice.
Age and the Systemic Response to Stroke

Aged Stroke

Young Stroke

Neat $10^{-2}$

![Graph comparing CFU/mL between Young Stroke and Aged Stroke](chart.png)
The amount AND the composition of systemic bacteria differ in young vs. aged mice

<table>
<thead>
<tr>
<th></th>
<th>Young Sham</th>
<th>Young Stroke</th>
<th>Aged Sham</th>
<th>Aged Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLN</td>
<td>1/7 14.3%</td>
<td>5/7 71.4%</td>
<td>3/8 37.5%</td>
<td>6/7 85.7%</td>
</tr>
<tr>
<td>Spleen</td>
<td>0/6 0%</td>
<td>4/10 40%</td>
<td>1/8 12.5%</td>
<td>6/7 85.7%</td>
</tr>
<tr>
<td>Liver</td>
<td>0/7 0%</td>
<td>8/10 80%</td>
<td>2/8 25%</td>
<td>7/7 100%</td>
</tr>
<tr>
<td>Lung</td>
<td>0/7 0%</td>
<td>3/10 30%</td>
<td>1/8 12.5%</td>
<td>5/7 71.4%</td>
</tr>
</tbody>
</table>

**Young Stroke**
- *Escherichia* (50%)
- *Stenotrophomonas* (6%)
- *Enterococcus* (13-17%)

**Aged Stroke**
- *Enterobacter* (50%)
Aging and stroke impair GI barrier function and allow for bacterial translocation.

Stroke-induced loss of the gut hypoxic barrier, O2 sensing pimonidazole (green)
A principle component analysis (PCA) showed significant separation between age groups (ANOSIM $p$ value = 0.005). Principle component 1 (PC1) explained 31.19% of variation seen in samples while PC2 (15.97%) further separated the different microbial populations from different microbiome. PCA plots were generated using the raw abundances of microbial groups after 16s rRNA sequencing.
Biome transfers influence behavioral recovery

[Bar charts showing latency to fall for young and aged mice 7 days after ischemic stroke or sham surgery, with significance marked by asterisks.]
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