Soluble ST2 Predicts Delayed Cerebral Ischemia & Outcome after Subarachnoid Hemorrhage

Disclosures

- National Institutes of Health
- American Heart Association
- Andrew David Heitman
  Neurovascular Research Foundation
Aneurysmal Subarachnoid Hemorrhage

- Approximate incidence is 1 per 10,000
- Mortality rate is approximately 30%
- Poor functional outcome in 10-20% of patients
- Several factors contribute:
  - Age
  - Initial aSAH severity
  - Delayed cerebral ischemia (DCI)
Background

- Neuroinflammatory responses have been implicated in the sequelae of aSAH
- sST2 is a decoy receptor that promotes immune activation of Th1 pro-inflammatory cells
- We have previously shown sST2 is linked to outcome after ischemic stroke
- We hypothesized that sST2 is a marker for neuroinflammation induced secondary injury in aSAH
SAH Cohort Design

**MGH cohort 2013-2016**
- non-traumatic SAH N=191
  - aSAH N=174
  - pSAH N=17
    - aSAH with samples N=169

**Copenhagen cohort 2014-2015**
- aSAH N=127
  - aSAH with EVD N=63
  - aSAH without EVD N=64
  - aSAH with samples N=50
SAH Cohort Design

MGH cohort
2014-2015

Copenhagen cohort
2014-2015
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MGH aSAH cohort</th>
<th>MGH pSAH cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=169</td>
<td>N=17</td>
</tr>
<tr>
<td>Age (yrs.)</td>
<td>57 ± 12</td>
<td>58 ± 8</td>
</tr>
<tr>
<td>Sex (F)</td>
<td>108 (64%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td>HH grade</td>
<td>2 [1, 4]</td>
<td>1 [1, 2]</td>
</tr>
<tr>
<td>modified Fisher score</td>
<td>3 [3, 4]</td>
<td>3 [2, 3]</td>
</tr>
<tr>
<td>Clipping</td>
<td>73 (43%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>mRS, 90 day</td>
<td>2 [1, 4]</td>
<td>1 [0, 1]</td>
</tr>
<tr>
<td>DCI</td>
<td>61 (47%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Age (yrs.)</td>
<td>57 ± 12</td>
<td>58 ± 8</td>
</tr>
</tbody>
</table>
sST2 over time

Plasma sST2 time course

CSF sST2 time course
sST2 predicts poor outcome (mRS 3-6) independent of clinical risk factors

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sST2*</td>
<td>3.02</td>
<td>1.58</td>
<td>5.76</td>
<td>0.001</td>
</tr>
<tr>
<td>+ Age, Sex, HH</td>
<td>2.50</td>
<td>1.22</td>
<td>5.11</td>
<td>0.012</td>
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<tr>
<td>+ Age, Sex, HH, mF</td>
<td>2.43</td>
<td>1.17</td>
<td>5.06</td>
<td>0.017</td>
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<tr>
<td>+ Age, Sex, HH, mF, Clip</td>
<td>2.58</td>
<td>1.20</td>
<td>5.56</td>
<td>0.015</td>
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<tr>
<td>+ Age, Sex, HH, mF, Clip, CHF</td>
<td>2.56</td>
<td>1.19</td>
<td>5.52</td>
<td>0.017</td>
</tr>
<tr>
<td>+ Age, Sex, HH, mF, Clip, CHF, Afib</td>
<td>2.54</td>
<td>1.17</td>
<td>5.49</td>
<td>0.018</td>
</tr>
</tbody>
</table>

* sST2 measured at day 3.5
sST2 predicts mortality independent of clinical risk factors

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower 95%</td>
<td>Upper 95%</td>
</tr>
<tr>
<td>sST2*</td>
<td>4.62</td>
<td>1.92</td>
<td>11.10</td>
</tr>
<tr>
<td>+ Age, Sex, HH</td>
<td>4.43</td>
<td>1.56</td>
<td>12.56</td>
</tr>
<tr>
<td>+ Age, Sex, HH, mF</td>
<td>4.38</td>
<td>1.49</td>
<td>12.86</td>
</tr>
<tr>
<td>+ Age, Sex, HH, mF, Clip</td>
<td>4.13</td>
<td>1.38</td>
<td>12.40</td>
</tr>
<tr>
<td>+ Age, Sex, HH, mF, Clip, CHF</td>
<td>3.90</td>
<td>1.30</td>
<td>11.73</td>
</tr>
<tr>
<td>+ Age, Sex, HH, mF, Clip, CHF, Afib</td>
<td>3.79</td>
<td>1.24</td>
<td>11.64</td>
</tr>
</tbody>
</table>

* sST2 measured at day 3.5
sST2 and Mortality

**Graph:**
- **Y-axis:** Survival Rate
- **X-axis:** Days until death
- **Legend:**
  - High sST2
  - Medium sST2
  - Low sST2

- **Data:** sST2 > 105 ng/mL

**Log-Rank:** $P < 0.0001$
SAH and secondary injury

- sST2
- DCI
- Outcome Mortality
Delayed cerebral ischemia: Focal neurological impairment, or a decrease of at least 2 points on the GCS not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes.
sST2 predicts future DCI

P = 0.0026

ROC threshold: sST2 > 77 ng/mL

* sST2 measured at day 3.5
## Copenhagen replication cohort

<table>
<thead>
<tr>
<th></th>
<th>Copenhagen aSAH cohort N=50</th>
<th>MGH aSAH cohort N=169</th>
<th>MGH pSAH cohort N=17</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>61 ± 11</td>
<td>57 ± 12</td>
<td>58 ± 8</td>
</tr>
<tr>
<td><strong>Sex (F)</strong></td>
<td>45 (90%)</td>
<td>108 (64%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td><strong>WFNS grade</strong></td>
<td>3 [1, 4]</td>
<td>2 [1, 4]</td>
<td>1 [1, 2]</td>
</tr>
<tr>
<td><strong>modified Fisher score</strong></td>
<td>3 [3, 3]</td>
<td>3 [3, 4]</td>
<td>3 [2, 3]</td>
</tr>
<tr>
<td><strong>Clipping</strong></td>
<td>14 (28%)</td>
<td>73 (43%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>mRS, 90 day</strong></td>
<td>1 [0, 3]</td>
<td>2 [1, 4]</td>
<td>1 [0, 1]</td>
</tr>
<tr>
<td><strong>DCI</strong></td>
<td>25 (50%)</td>
<td>61 (47%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
sST2 replication cohort

sST2 predicts poor outcome (mRS 3-6)

\[ P = 0.025 \]
sST2 replication cohort

sST2 predicts DCI

Day

sST2 (ng/mL)

P = 0.0045
Summary

- sST2 demonstrates an early rise in plasma and CSF that peaks at ~day 1-3
- Higher sST2 level predicts poor outcome and mortality
- Higher sST2 level predicts DCI
- sST2 is also linked to outcome after ischemic stroke and intracerebral hemorrhage*
- We hypothesize that sST2 is a marker for neuroinflammation induced secondary brain injury

*Poster #: WMP101; Wednesday 5:30-6:30 pm
Acknowledgements

- Andrew David Heitman Neurological Research Foundation
  - Research Staff
  - Research Participants
- MGH Neurosciences ICU
- Rigshospitalet Hospital Neurosciences ICU
- Center for Genomic Medicine
  - Rosand Lab
- Kimberly Lab