Cerebrospinal Fluid Analysis in Acute Human Spinal Cord Injury: Assessment of Inflammatory Cytokines and Development of Injury Severity Biomarkers

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Introduction: An important barrier to the SCI community in its search for therapies has been the paucity of knowledge about the pathophysiology of human SCI (in contrast to animal SCI). An important challenge in human SCI clinical trials has been our reliance upon functional measures (ie. the neurologic examination) for stratifying the severity of paralysis. This study addresses both obstacles, by characterizing the inflammatory response to human SCI, and establishing biological correlates to injury severity. The purposes of this study were to 1. describe the temporal pattern of expression of inflammatory cytokines and other neuronal proteins in the cerebrospinal fluid of human patients with acute spinal cord injury, and to 2. develop biological surrogates that could be used to characterize injury severity and predict neurologic outcome

Methods: 15 cervical and 5 thoracic SCI patients within 48 hours of sustaining a complete (ASIA A) or incomplete (ASIA B or C) injury were enrolled in a clinical trial in which an intrathecal catheter was inserted to drain CSF for 72 hours. Cytokines were measured in CSF and serum samples using a multiplex cytokine array system and standard ELISA techniques. CSF of patients undergoing joint replacements under spinal anesthesia served as controls.

Results: IL-6, IL-8, IP-10, MCP-1, TNF-R1, and tau were elevated within 24 hours after SCI and tended to decrease over the next 72 hours (Fig 1). IL-6, IL-8, MCP-1, and tau were elevated in a severity-dependent fashion (ie. higher in ASIA A injuries than B or C injuries). A model was generated using IL-6, IL-8, and MCP-1 to predict injury severity (ASIA A, B, or C). After inputting the observed CSF concentrations into this model, the model was able to accurately predict the patients’ ASIA grade with a rate of 84.2% (Fig 2). Using receiver operating characteristics (ROC) analysis, the area under the curve (AUC) or C-index for this prediction model was 0.95 (with a perfect model having an AUC of 1.0). Furthermore, for patients with cervical cord injuries, the cytokine levels were more accurate than their ASIA grade at predicting the extent of segmental motor recovery at 6 months post-injury (when the majority of segmental recovery has occurred). For predicting segmental motor recovery at either 0-4 motor points, 5-10 motor points, or greater than 10 motor points, the AUC of the cytokine

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**Conclusions:** The temporal expression pattern of a number of inflammatory cytokines such as IL-6, IL-8, and MCP-1 provides invaluable information about the of human SCI, and gives us the ability to make comparisons with the animal condition. Additionally, a combination of these cytokines appear to be expressed in an injury-severity dependent fashion. This is the first ever description of the temporal pattern of change in inflammatory cytokine expression after human SCI. Additionally, our prediction model represents the first biological surrogates of cord injury that may be used to more accurately predict injury severity and stratify patients for clinical trials.

**Figure 1**

![Calculated trend plots of IL-6, IL-8, MCP-1, and Tau, demonstrating a severity-dependent expression](image)

**Figure 2**

<p>| Injury Severity Prediction Based Upon IL-6, IL-8, and tau Levels from CSF Sample at 24 Hours Post-Injury |</p>
<table>
<thead>
<tr>
<th>PREDICTED</th>
<th>OBSERVED</th>
<th>ASIA A</th>
<th>ASIA B</th>
<th>ASIA C</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASIA A</td>
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<td>1</td>
<td>0</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>ASIA B</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>ASIA C</td>
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<td>0</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>4</td>
<td>3</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

Note 1: Patient 9 did not have a CSF sample taken at 24 hours, so the total n = 19

Note 2: the overall prediction rate is \((10+3+3)/19 = 16/19 = 84.2\%\)

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