Biomarkers for Head Injury – Should We Routinely Order?

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Objectives

- Discuss potential benefits of biomarkers for diagnosing and treating head injury
- Briefly review the pathophysiology of mild traumatic brain injury (mTBI)/concussion
- Discuss current research for most promising biomarkers
- Review the current position statements
- Where are we headed?
Why biomarkers?

- Diagnosing mTBI is dependent on subjective reporting of symptoms
  - Potentially influenced by motivation to conceal or embellish signs or symptoms
  - Potentially influenced by inability of patient to appreciate subtle differences in symptomatology
- Assist with prognosis
- Guide return to play decisions
Pathophysiology: sites of cell injury
Numerous potential biomarkers

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Potential fluid biomarkers of mild TBI</th>
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<tbody>
<tr>
<td>Marker</td>
<td>Process or structure affected</td>
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<tr>
<td>Cerebrospinal fluid:serum albumin ratio</td>
<td>Blood-brain barrier</td>
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<tr>
<td>Interleukins and other acute-phase inflammatory response proteins</td>
<td>Neuroinflammation</td>
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<tr>
<td>Total tau protein</td>
<td>Axon</td>
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<tr>
<td>Myelin basic protein</td>
<td>Axon</td>
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<tr>
<td>Neurofilament light polypeptide</td>
<td>Axon</td>
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<tr>
<td>Neurofilament heavy polypeptide</td>
<td>Axon</td>
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<tr>
<td>(\gamma)-Enolase</td>
<td>Neuron</td>
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<tr>
<td>S100-B</td>
<td>Astroglial cells</td>
</tr>
<tr>
<td>Glial fibrillary acidic protein</td>
<td>Astroglial cells</td>
</tr>
<tr>
<td>Secreted APP(\alpha) and APP(\beta)</td>
<td>Axon</td>
</tr>
<tr>
<td>Amyloid(\beta_{40}) and amyloid(\beta_{42})</td>
<td>Plaque pathology</td>
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<tr>
<td>Spectrin breakdown products</td>
<td>Neuron</td>
</tr>
<tr>
<td>Ubiquitin carboxyl-terminal hydrolase isoenzyme L1</td>
<td>Neuron</td>
</tr>
<tr>
<td>Peripheral blood mononuclear small noncoding RNA molecules</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**Abbreviations:** APP, amyloid precursor protein; NA, not available; TBI, traumatic brain injury.
Limitations of biomarkers

• Blood-Brain barrier
  • impaired integrity only in more severe TBI

• Dilution in the much larger plasma volume and extracellular matrix of peripheral tissues

• Proteolytic degradation

• Renal or Hepatic clearance

• Binding to carrier proteins
Most promising biomarkers

- **S-100B**: marker of glial injury
- **T-Tau**: marker of axonal damage
- **Neuron-specific enolase**: marker of neuronal injury
- **Apoa-1**: marker of blood-brain barrier injury

- serum analysis of concentrations of two biochemical markers of brain tissue damage, \textbf{S-100B} and \textbf{NSE} (neurone-specific enolase) in male soccer players

- Blood samples were taken in players before and after a competitive game and the numbers of headers and of trauma events during soccer play were assessed

- Both S-100B and NSE were significantly raised in serum samples obtained after the game in comparison with the pre-game values

- Only changes in S-100B concentrations (post-game minus pre-game values) were statistically significantly correlated to the number of headers

- Concentrations of S-100B also had some correlation with the number of other trauma events

- Preseason blood samples evaluated for levels of **T-tau, NSE, and S-100B** in 288 hockey players from 12 teams of the top professional ice hockey league in Sweden during the 2012-2013 season

- Thirty-five concussed players had repeat blood testing at 1, 12, 36, and 144 hrs after concussion

- Concussed players T-tau (median, 10.0 pg/mL; range, 2.0-102 pg/mL) compared with preseason values (median, 4.5 pg/mL; range, 0.06-22.7 pg/mL) (P < .001).

- The levels of the astroglial injury biomarker S-100B were also increased in players with sports-related concussion (median, 0.075 μg/L; range, 0.037-0.24 μg/L) compared with preseason values (median, 0.045 μg/L; range, 0.005-0.45 μg/L) (P < .001)

- The highest biomarker concentrations of total tau and S-100 calcium-binding protein B were measured immediately after a concussion, and they decreased during rehabilitation.

- There were NO significant changes detected in the levels of neuron-specific enolase from preseason values (median, 6.5 μg/L; range, 3.45-18.0 μg/L) to postconcussion values (median, 6.1 μg/L; range, 3.6-12.8 μg/L) (P = .10)
Prospective, multi-centered study of 787 patients with mTBI who presented to the emergency department within 6 h of injury and 467 controls who presented to the outpatient laboratory for routine blood work.

Serum was analyzed for S100B and apoA.

At cutoff values defined by 90% of controls:
- the specificity for mTBI using S100B 89.9% and the sensitivity using S100B 25.2%
- similarly, apoA-I had a specificity of 90.2% and specificity of 24.9%
- There was significant age and race-related variation in the accuracy of S100B for the diagnosis of mTBI.

The combined use of serum S100B and apoA-I maximizes classification accuracy for mTBI.
- systematic review of 11 prospective cohort studies that assessed the ability of serum biomarkers to predict Postconcussive Syndrome (PCS) after mTBI
  - S100 proteins
  - cleaved Tau proteins
  - NSE

- concluded that no biomarker consistently demonstrated the ability to predict PCS after MTBI

  - but that combination of clinical factors with biomarkers could together more accurately predict PCS
Systematic review of experimental, observational, case control studies from 1966 – 2013, 52 studies were identified 13 were reviewed

There were eleven different biomarkers assessed: including S100β, NSE, tau, prolactin, GFAP, NFL, amyloid beta, BDNF, CK and h-FABP, cortisol, and albumin

-Conclusion: a handful of biomarkers showed correlation with number of hits to the head (soccer), acceleration/deceleration forces (jumps, collisions, and falls), post-concussive symptoms, trauma to the body versus the head

-- Although there are no validated biomarkers for concussion yet, there is potential for biomarkers to provide diagnostic, prognostic, and monitoring information post-injury. They could also be combined with neuroimaging to assess injury evolution and recovery.
- “Evolving technologies for the diagnosis of concussion, such as newer neuroimaging techniques or biological markers, may provide new insights into the evaluation and management of sports concussion.”
Summary of Objectives

• What are potential benefits of biomarkers for diagnosing and treating head injury?
  • Potential for diagnostic and prognostic value
  • Reviewed the pathophysiology of mild traumatic brain injury (mTBI)/concussion and discussed current research for most promising biomarkers
    • S-100B seems to be the most promising
    • Tau, Apoa, NSE also have potential
  • Review the current position statements
  • Where are we headed?


NIH Neurological Disorders and Stroke, pilot study being done, through NFL funding, study “Cortical GABA in Pediatric Sports Concussion” ongoing serum and CSF