Neuroendocrine Consequences Following Traumatic Brain Injury

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• Served on the advisory boards for Pfizer, Novo Nordisk, Sanofi and Corcept Therapeutics
Outline

• Epidemiology of TBI
• Pathophysiology of TBI-induced hypopituitarism
• Neuroendocrine dysfunction in the acute phase of TBI
• Neuroendocrine dysfunction in the chronic phase of TBI
• Natural history of TBI-induced hypopituitarism
• TBI in special populations
• Screening for TBI-induced hypopituitarism
Epidemiology

• ~180-250 persons per 100,000 per year die or hospitalized
• In the US in 2003, ~1.5 million TBI cases per year
  - 1.2 million ER visits
  - 290,000 hospitalizations
  - 51,000 deaths
  - ~2% of the population living with the consequences of TBI
  - lifetime cost of $600,000 to $1.9 million per person

• At risk groups
  - males 2x to females
  - aged 15-24 yrs
  - children < 5 yrs
  - aged > 75 yrs

Rutland-Brown W et al. J Head Trauma Rehabil 2006;21:544-548
Causes

Based on CDC data, 2006

- Falls: 28%
- Traffic accident deaths: 20%
- Violence related: 19%
- Assaults: 11%
- Unknown: 9%
- Other transport: 2%
- Bicycle (non MV): 3%
- Other: 7%
- Suicide: 1%
Glasgow Coma Scale

Eye Opening Response
• Spontaneous—open with blinking at baseline 4 points
• To verbal stimuli, command, speech 3 points
• To pain only (not applied to face) 2 points
• No response 1 point

Verbal Response
• Oriented 5 points
• Confused conversation, but able to answer questions 4 points
• Inappropriate words 3 points
• Incomprehensible speech 2 points
• No response 1 point

Motor Response
• Obeys commands for movement 6 points
• Purposeful movement to painful stimulus 5 points
• Withdraws in response to pain 4 points
• Flexion in response to pain (de corticate posturing) 3 points
• Extension response in response to pain (decerebrate posturing) 2 points
• No response 1 point

Classification:
GCS 13-14: Mild  GCS 9-12: Moderate  GCS 3-9: Severe
Pathophysiology

Acute phase

Potential mechanisms

• Vascular injury to the hypothalamus and/or pituitary
• Direct mechanical injury to the hypothalamus, pituitary stalk and/or pituitary gland itself
• Compression of the pituitary gland, hypothalamic nuclei, or disruption of the long hypophyseal vessels by edema, hemorrhage, skull fracture, or raised ICP
• Ischemia and infarction from hypoxia, hypotension, anemia and transection of hypophyseal vessels
• Diffuse axonal injury
Arteries and Veins of Hypothalamus and Hypophysis

- Hypothalamic vessels
- Superior hypophyseal artery
- Artery of trabecula
- Trabecula (fibrous tissue)
- Secondary plexus of hypophyseal portal system
- Adenohypophysis (anterior lobe of pituitary gland)
- Efferent hypophyseal vein to cavernous sinus
- Infraportal sinusoids
- Inferior hypophyseal artery
- Primary plexus of hypophyseal portal system
- Long hypophyseal portal veins
- Short hypophyseal portal veins
- Efferent hypophyseal vein to cavernous sinus
- Neurohypophysis (posterior lobe of pituitary gland)
- Capillary plexus of infundibular process
- Efferent hypophyseal veins to cavernous sinus
Histologic studies of the pituitary gland in acute TBI

Normal adenohypophysis

Extensive infarct of the adenohypophysis
Pathophysiology

Chronic phase

- Inflammatory mediators (cytokines, free radicals, amino acids, nitric oxide) and excitatory amino acids (N-methyl-D-aspartate)
- Development of antibodies to pituitary (APA) and hypothalamus (AHA)
  - found in ~20% of boxers
  - pituitary dysfunction more prevalent in strongly APA and AHA positive patients 5 yrs after TBI
Serum sample positive antibodies to pituitary cells detected by immunofluorescence in a TBI patient at the 5th yr compared to a negative control serum

Pathophysiology

Genetics

• ApoE-ε4 is associated with Alzheimer’s disease and a poorer outcome after TBI
• Evidence that ApoE-ε3/ε3 genotype (17.7%) may be associated with a reduced risk of TBI-induced hypopituitarism than in other genotypes (42%; P = 0.01)

Neuroendocrine dysfunction in the acute phase of TBI

Neuroendocrine dysfunction in the chronic phase of TBI

Agha A et al. J Clin Endocrinol Metab 2004;89:4929-4936
Natural history of TBI-induced hypopituitarism (1)

- Anterior pituitary hormone deficiencies that occur soon after TBI recover in some patients, usually by 6 mths
- Gonadotropin deficiency and hyperprolactinemia most likely to recover in majority of patients
- Some patients may develop delayed secondary AI (6-12 mths after TBI)
- A recovery of GH secretion in 66% and cortisol secretion in 50% have been reported
Natural history of TBI-induced hypopituitarism (2)

Natural history of TBI-induced hypopituitarism (3)

Hypothalamic-pituitary dysfunction following TBI: a systematic review.

• Examined 14 studies of 1015 patients
• Prevalence of pituitary dysfunction 15-68%
  - severe 35.3%
  - moderate 10.9%
  - mild 16.8%
• Trend toward improvement of pituitary function over time, but in some cases, new deficiencies evolved in chronic phase
• In 809 patients studied > 4 mths, the following were noted:
  - GH 12%
  - LH/FSH 12%
  - ACTH 8%
  - TSH 4%
  - Multiple deficiencies 8%

Schneider HJ et al. JAMA 2007;298(12):1429-1438
IGF-I levels After TBI

Male LH, FSH and Testosterone levels After TBI

Quality of Life After TBI

Lipids After TBI

Body Composition After TBI

Long-Term Brain Damage and Hypopituitarism

- 55 patients studied at least 1 year after TBI
- All had cognitive or behavioral disorders

<table>
<thead>
<tr>
<th>Frequency of pituitary deficits</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 deficit</td>
<td>42</td>
<td>76.4</td>
</tr>
<tr>
<td>Global GH deficiency</td>
<td>35</td>
<td>63.6</td>
</tr>
<tr>
<td>Partial GH deficiency</td>
<td>13</td>
<td>23.6</td>
</tr>
<tr>
<td>Severe GH deficiency</td>
<td>22</td>
<td>40.0</td>
</tr>
<tr>
<td>ACTH deficit</td>
<td>15</td>
<td>27.3</td>
</tr>
<tr>
<td>TSH deficit</td>
<td>12</td>
<td>21.8</td>
</tr>
<tr>
<td>Gonadotropin deficit</td>
<td>1</td>
<td>3.6</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>4</td>
<td>7.3</td>
</tr>
<tr>
<td>SIADH</td>
<td>1</td>
<td>1.8</td>
</tr>
</tbody>
</table>

## Similarities of complaints of patients with TBI and adult-onset GH deficiency

<table>
<thead>
<tr>
<th>Complaints</th>
<th>Moderate to severe TBI</th>
<th>Adult-onset GH deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory impairment</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Concentration impairment</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Decreased IQ</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Impaired judgment</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Poor organizational skills</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Decreased quality of life</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fatigue</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anxiety</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Depression</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Social isolation</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Increased unemployment</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Hypopituitarism and Sports TBI: NFL (1)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD or Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>69</td>
</tr>
<tr>
<td>Age</td>
<td>47.3 ± 10.2 (30 – 65)</td>
</tr>
<tr>
<td>BMI</td>
<td>33.8 ± 6.0 (24 – 51)</td>
</tr>
<tr>
<td>Years since retirement</td>
<td>18.5 (2 – 41)</td>
</tr>
<tr>
<td>Years in NFL</td>
<td>5 (1 – 17)</td>
</tr>
<tr>
<td>NFL games played</td>
<td>54 (0 – 241)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GH deficiency</td>
<td>13 (19.1%)</td>
</tr>
<tr>
<td>Testosterone deficiency</td>
<td>6 (8.8%)</td>
</tr>
<tr>
<td>GH and Testosterone deficiency</td>
<td>3 (4.4%)</td>
</tr>
<tr>
<td>Any hormonal deficiency</td>
<td>16 (23.5%)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>34 (50.0%)</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>45 (66.2%)</td>
</tr>
</tbody>
</table>

### Hypopituitarism and Sports TBI: NFL (2)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Non-deficient (n=52)</th>
<th>Deficient (n=16)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QoL: SF-36 MCS (mean ± SD)</strong></td>
<td>37.4 ± 9.6</td>
<td>32.9 ± 10.5</td>
<td>0.113</td>
</tr>
<tr>
<td><strong>QoL: SF-36 PCS (mean ± SD)</strong></td>
<td>43.0 ± 10.5</td>
<td>44.1 ± 13.4</td>
<td>0.740</td>
</tr>
<tr>
<td>Erectile dysfunction (IIEF) &lt; 25</td>
<td>9.8%</td>
<td>18.8%</td>
<td>0.336</td>
</tr>
<tr>
<td>Erectile function score (mean ± SD)</td>
<td>55.2 ± 16.8</td>
<td>42.8 ± 20.0</td>
<td><strong>0.016</strong></td>
</tr>
</tbody>
</table>
Hypopituitarism and Sports TBI: Kickboxing

- GH deficiency in 5/22 and ACTH deficiency in 2/22
- In those that were GH deficient, there was also impaired cognitive performance
- Serum IGF-I level correlated with the number of bouts

Hypopituitarism and Sports TBI: Boxing (1)

- GH deficiency in 5/11 amateur boxers
- Prevalence of GH deficiency correlated with the number of bouts and duration of boxing

Hypopituitarism and Sports TBI: Boxing (2)

**Age categories (n = 61)**
- young boxers (n = 21): mean age 18 yrs (range: 17-19 yrs)
- adult boxers (n = 23): mean age 22 yrs (range: 19-28 yrs)
- retired boxers (n = 17): mean age 42 yrs (range: 32-53 yrs)

- GH deficiency in 15% and ACTH deficiency in 8%, with hypopituitarism more common in retired than active boxers
- Mean pituitary volume more common lower in adult (446 mm³) and retired (423 mm³) boxers than in young boxers (681 mm³) boxers (P = 0.001)
- P-300 auditory event-related potential (ERP) measure is widely used to evaluate cognitive performance; P300 amplitudes were lower at all electrode sites in the GH-deficient group of boxers and kickboxers

Hypopituitarism and TBI: Soldiers

- Basal pituitary and target-hormone hormone levels were measured in 2 groups of subjects: blast-related mild TBI ≥ 1 yr (n=26) vs deployment controls (n=7)
- 11/46 (42%) of subjects with blast-related mild TBI had ≥ 1 pituitary hormone hormone deficits: GH deficiency (n=5), hypogonadism (n=3)

GH therapy in adult GH deficient TBI patients

- **German KIMS database (GH & IGF Res 2010)**
  - 84 GH-deficient adults in the database
  - QoL improved after 1 yr of GH therapy comparable to other causes of GH deficiency subjects
- **Case report (Brain Injury 2010)**
  - 43 yo female with improvements in muscle force production, body composition, and aerobic capacity, but none in cognition after 1 yr of GH therapy
- **Psychiatric changes (J Endocrinol Invest 2010)**
  - Decreased depression and other psychiatric symptoms in 6 subjects after 1 yr of GH therapy
- **Cognitive changes (J Neurotrauma 2010)**
  - Some of the cognitive impairments in 23 persons with GHD/GHI after TBI where partially reversed after 1 yr of GH therapy
- **Physical and psychological disability (J Neurotrauma 2014)**
  - 23 patients received GH therapy and 27 patients untreated
  - Greatest improvement in QoL and cognition in those with lowest baseline performance
Caveats Regarding TBI and Hypopituitarism Studies

Heterogeneity of TBI
- what produced the injury
- how severe is the injury
- what part of the brain is affected
- was it a penetrating injury

TBI is an evolving process
- how much time has elapsed since the injury
- how much CNS function is recovered
- what other injuries were sustained

Repeated TBI
Sub-concussive TBI
Factors Complicating Pituitary Assessment After TBI

- Brain injury event itself
- Medications and anesthesia used to treat TBI
  - glucocorticoids inhibits CRH-ACTH-cortisol axis and TSH release
  - opioids inhibit GnRH-LH-T axis
- Sequelae such as hypotension and hypoxemia
- Stress response to illness
- Sleep disruption in the ICU
- Undernutrition with IV fluids while NPO
- Inability to perform stimulation tests
Screening of Pituitary Function After TBI (1)

• Who should be tested?
  - all patients with moderate to severe TBI
  - patients with concussions requiring hospitalization for > 24h
  - patients with mild TBI if clinically indicated based on signs and symptoms
  - susceptible patients, e.g. basal skull fracture and older age group
  - patients with abnormality on initial CT (brain swelling, diffuse axonal injury, epidural or subdural hematoma)

• Special circumstances
  - TBI patients in vegetative state and severe disability without clinical findings of hypopituitarism
Screening of Pituitary Function After TBI (2)

• **When and how screening should be performed?**
  - important not to miss adrenal insufficiency and diabetes insipidus
  - reassess at 3 or 6 mths and 12 mths after TBI, then annually until 3rd yr post-TBI
Proposed Algorithm for Screening of Pituitary Function After Mild TBI

Patients with MTBI

- Assess ACTH deficiency by measuring morning basal cortisol levels in the acute phase (particularly in the first days after trauma), and TSH deficiency before discharge

Treat ACTH and TSH deficiencies

- Reassess at 3 or 6 months and 12 months (baseline hormonal work-up, dynamic test for ACTH deficiency and GHD)

No hormone deficiencies

Reassess yearly intervals until third year post TBI (baseline hormonal work-up; rarely new onset hormonal deficiencies may develop)

One or more hormone deficiencies

Treat TSH, Gonadotropin and ACTH deficiencies other than isolated GHD

Reassess yearly intervals until third year post TBI (baseline hormonal work-up, dynamic test for ACTH deficiency and GHD)

Recommended Endocrine Tests (1)

• **GH deficiency**
  - IGF-I: below or low normal age-related reference range
  - consider GH stimulation testing: insulin tolerance test, glucagon test

• **Gonadal deficiency**
  - basal LH, FSH, and estradiol/AM testosterone

• **ACTH deficiency**
  - AM ACTH: below or low normal reference range
  - AM cortisol: < 5 µg/dL ACTH deficiency; > 15 µg/dL normal axis
  - consider 1 µg ACTH stimulation test if AM cortisol 5-15 µg/dL
Recommended Endocrine Tests (2)

• **TSH deficiency**
  - TSH and free T4: inappropriately low or normal TSH with low free T4

• **AVP deficiency**
  - paired urine and plasma osmolalities (urine volume > 40 ml/kg/day; urine osmolality < 300 mosm/kg H₂O and hypernatremia)
  - water deprivation test

• **Other labs**
  - check prolactin, fasting glucose, HbA1c, fasting lipids, calcium, and vitamin 25OHD
Conclusions

• TBI is a common injury, especially among children, young adults and elderly
• Varying degrees of hypopituitarism occur after TBI
• Use of hormones as biomarkers to evaluate for recovery from TBI has not been fully explored
• Natural Hx of TBI-induced endocrinopathy not well understood
• Screening programs to detect TBI-induced hypopituitarism need to become part of standard clinical care
• Hormone replacement therapy in acute and in recovery phase from TBI has the potential to reduce morbidity and improve outcomes
• Multidisciplinary team involvement
The most important thing is not to stop questioning. Curiosity has its own reason for existing.

*Albert Einstein*

THANK YOU!