6th Annual Intensive Update in Neurology

September 16, 2016

Neuroendocrine Consequences After Traumatic Brain Injury

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Disclosures

• Received research grants from Pfizer, Novo Nordisk, Eli Lilly, Versartis, Teva and Prolor Biotech

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

• Epidemiology of TBI

• Pathophysiology of TBI-induced hypopituitarism

• Neuroendocrine dysfunction of TBI

• TBI in special populations

• Screening for TBI-induced hypopituitarism

• Case
Epidemiology

• 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

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

Based on CDC data, 2006
Trends in Visits for TBI to ER Departments in the US

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
- Obey commands for movement 6 points
- Purposeful movement to painful stimulus 5 points
- Withdraws in response to pain 4 points
- Flexion in response to pain (decorticate 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
Pituitary gland: normal and effects of trauma
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)
Serum sample positive antibodies to pituitary cells detected by immunofluorescence in a TBI patient at the 5\textsuperscript{th} yr compared to a negative control serum

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 2014

• Examined 66 studies of 5386 patients

• ~30% of TBI patients have persistent anterior pituitary hormone disorders

• Older age, TBI severity and skull fractures are risk factors

• Endocrine disorders associated with higher ICU mortality

Quality of Life After TBI

Body Composition After TBI

## 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD or Median (range)</th>
</tr>
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<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>
</tr>
</thead>
<tbody>
<tr>
<td>GH deficiency</td>
</tr>
<tr>
<td>Testosterone deficiency</td>
</tr>
<tr>
<td>GH and testosterone deficiency</td>
</tr>
<tr>
<td>Any hormonal deficiency</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
</tr>
</tbody>
</table>

Kelly D et al. J Neurotrauma 2014 Jul 1;31(13):1161-71
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**

**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 lower in adult (446 mm$^3$) and retired (423 mm$^3$) boxers than in young (681 mm$^3$) boxers (P = 0.001)
- Cognitive performance lower in the GH-deficient group than the GH-sufficient boxers

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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 deficits

GH therapy in adult GH deficient TBI patients

- **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 were 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

- **Quality of life (Eur J Endocrinol 2015)**
  - Compared to NFPA, 126 TBI patients had worse QoL, and when treated with GH replacement achieved long-term benefit in QoL
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

• Sequelae such as hypotension and hypoxemia

• Stress response to illness

• Sleep disruption in the ICU

• Undernutrition with IV fluids while NPO
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
  - susceptible patients, e.g. basal skull fracture and older patients
  - 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
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
Diabetes Insipidus and Lower Cortisol Levels Associated with Higher Mortality

Patients who developed DI had a significantly higher mortality than those who did not [17/51 (33.3%) vs 2/49 (4.1%), $P < 0.0002$].

Case (1)

Presentation

• 45 yr old male
• Involved in MVA
• GCS 8 on admission
• SAH on CT, pneumothorax and fractured R clavicle

Treatment

• Intubated and fluid resuscitated
• Meds: Pantoprazole, midazolam and opioids PRN
• BP 100-110/60-70 mmHg
• UO 100-150 ml/hr
Case (2)

- Hyponatremia during the 1st week
  - serum sodium 123-126 mmol/L
- Serum potassium 4.2 mmol/L and plasma glucose 82 mg/dL
- Urine sodium 44 mmol/L
- Urine osmolality 460 mOsm/kg

Possible causes of hyponatremia
- SIADH
- Adrenal insufficiency
- Hypothyroidism
- Cerebral salt wasting
Case (3)

- Measure serum AM ACTH and AM cortisol
- Restrict fluids
- Consider hypertonic saline
- Administer IV Hydrocortisone

**Lab results:**

- AM serum cortisol 3.6 µg/dL
- TSH 1.8 µg/mL (normal 0.4-4.5 µg/ml)
- Free T4 1.2 ng/dL (normal 0.9-1.8 ng/dL)

MRI brain no sellar mass
Case (4)

- Hydrocortisone was administered IV then PO
- Hyponatremia resolved after 48 hrs

- Subsequently noted to have UO > 300 ml/hr
- Serum sodium rose to 147 mmol/L
- Serum potassium, calcium and glucose were normal
- Urine osmolality 180 mOsm/kg

_Treatment: DDAVP, monitor fluid balance and serum sodium levels_
Case (5)

Re-evaluated 3 months after the TBI, persistent fatigue, low libido and depressed mood

- TSH 1.2 µg/mL (normal 0.4-4.5 µg/mL)
- Free T4 0.9 ng/dL (normal 0.9-1.8 ng/dL)
- AM testosterone 298 ng/dL and 262 ng/dL
- LH 2.5 U/L and FSH 1.6 U/L

Treatment: Levothyroxine and Androgel
Case (6)

Re-evaluated 7 months after the TBI, persistent fatigue and depressed mood, but libido somewhat improved

- IGF-I 105 ng/mL (normal 90-360 ng/mL)
- Glucagon stimulation test: peak GH 0.9 ng/mL

*Treatment: daily GH SC injections, continued on Hydrocortisone, Levothyroxine and Androgel*

Re-evaluated 12 months after TBI, all hormonal deficiencies persisted
Recommended Endocrine Tests (1)

• ACTH deficiency
  - AM ACTH: below or low normal reference range
  - AM cortisol: < 8 µg/dL ACTH deficiency; > 15 µg/dL normal axis
  - consider ACTH stimulation test if AM cortisol 8-15 µg/dL

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

• AVP deficiency
  - paired urine and plasma osmolalities
  - water deprivation test
Recommended Endocrine Tests (2)

• **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

• **Other labs**
  - check prolactin, fasting glucose, HbA1c, fasting lipids, calcium, and vitamin 25OHD
Management of Central Hypoadrenalism

• **Acute management**
  - Hydrocortisone 50-100 mg IV Q6-8hrs
  - Supportive care

• **Maintenance therapy (one of the following)**
  - Hydrocortisone 15-25 mg PO daily in 2-3 divided doses
  - dose adjustment based on clinical criteria (avoid excess)
  - sick day rules and Medic Alert bracelet advised

*No need for mineralocorticoid replacement*
Central Hypoadrenalism

Summary

- Central hypoadrenalism should always be considered in hospitalized TBI patients and hyponatremia or hemodynamic instability.

- Lower cortisol levels (< 8.6 µg/dL) in patients with TBI associated with higher mortality.

- Dynamic testing is neither helpful nor practical in patients with acute TBI.

- Glucocorticoid replacement is imperative in patients with suggestive findings and non-reassuring cortisol levels.
Management of Diabetes Insipidus

**Acute management**

- DDAVP 1-2 mcg SC or IV Q8-24hrs as needed
- Close monitoring of serum sodium and fluid balance

**Chronic management**

- DDAVP 0.1-0.2 mg PO once or twice daily
- Allowing the effect of the medication to wear off between doses may help avoid hyponatremia
- Patients with intact thirst should be allowed to drink to thirst; patients with impaired thirst needs to drink on schedule and require close monitoring of fluid balance
Diabetes Insipidus

Summary

- Central DI should be suspected in patients with TBI who are polyuric, polydipsic and/or hypernatremic

- Water deprivation test should only be performed in stable outpatients

- DDAVP should only be used as needed in hospitalized patients
Thyroid, Gonadal and Growth Hormone Replacement

- **Thyroid**
  - unless pre-existing hypothyroidism present, assessment of thyroid status should be deferred for 1-2 mths after TBI
  - glucocorticoid replacement first, then only LT4 replacement

- **Gonadal**
  - assess gonadal status should be deferred for 1-2 mths after TBI
  - testosterone replacement in men, estrogens in women

- **GH**
  - ensure adequate thyroid, glucocorticoid and gonadal hormone replacement before starting GH replacement
Conclusions

• TBI is a common injury, especially among children, young adults and elderly
• Varying degrees of hypopituitarism occur after TBI
• 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!