Pituitary Dysfunction after TBI
Randall Benson, M.D.
Center for Neurological Studies
Detroit, MI

"PERSISTENT POSTCONCUSSIVE SYNDROME"

- 19-year-old, 6'10" high school football player, 21 months post rear-end MVA by a semi. His car rolled over with partial collapse of the roof.
- Questionable LOC but brief posttraumatic amnesia
- Dazed and confused for a couple of days and then headache, nausea, neck pain, dizziness and fatigue.
- Cognitive symptoms: limited attention and concentration, difficulty multitasking. He had not been able to graduate despite now working from home on online courses.
- Spends most of his time in his dark basement.
- Could not generate one word on letter fluency task!
HISTORY OF TRAUMATIC HYPOPITUITARISM

- 1918—Case report in case of basilar skull fracture (German)
- 1942—Traumatic hypopituitarism reported only in 0.7%
- 1963—A case of panhypopituitarism in a man caused by a traumatic hypothalamic lesion
- 1979—Traumatic hypopituitarism: anterior hypophyseal insufficiency from indirect cranial trauma.
- 2004—Hypopituitarism as a consequence of traumatic brain injury (TBI) and its possible relation with cognitive disabilities and mental distress.
- 2005—Consensus guidelines on screening for hypopituitarism following traumatic brain injury.

REPORTS OF DEFICIENCY BY HORMONE

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<tr>
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<tbody>
<tr>
<td>GH</td>
<td>50%</td>
<td>60%</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>40%</td>
<td>50%</td>
<td>60%</td>
<td></td>
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<tr>
<td>TSH</td>
<td>30%</td>
<td>40%</td>
<td>50%</td>
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<tr>
<td>PRL</td>
<td>20%</td>
<td>30%</td>
<td>40%</td>
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SUMMARY FACTS

- Anterior pituitary dysfunction reported in 28-80% of people with TBI
- Longitudinal studies: 33-56% at 3 months; 23-36% at 12 months
- Does not correlate well with TBI severity
- Rate of hypopituitarism increases with repetitive head trauma, e.g., football, boxing.
- Presents in the first year post injury, GH and 21-hydroxylase highest rate of spontaneous resolution
- Isolated is 2-3 times more common than multiple hormone deficiencies.
- Growth hormone most often involved, due to long veins which are more vulnerable than short veins.
SIGNS AND SYMPTOMS OF LOW GH
- Increased fat mass (especially central adiposity)
- Decreased lean muscle mass
- Diminished muscle strength, physical energy and stamina
- Lack of motivation
- Lethargy
- Lack of vitality (changes in mood)
- Depression
- Impairment of cognitive function

SYMPTOMS OF LOW CORTISOL
- Mental and psychological ailments such as depression
- Fainting and dizziness
- Weakness and fatigue
- Emotional hypersensitivity
- Inability to cope with stress
- Social anxiety
- Muscle weakness
- Headache, scalp ache, or general body ache
- Extremely sensitive skin
- Nausea, diarrhea, and vomiting
- Abdominal pain and hunger pain despite an empty stomach
- Anxiety and jitters
- Clumsiness and confusion
- Motion sickness
- Insomnia and dark circles under the eyes
- Low bladder capacity and symptoms of IBS
- Irregular or non-existent menstrual period

SYMPTOMS OF LOW THYROID
- Fatigue
- Weakness
- Weight gain or difficulty losing weight (despite reduced food intake)
- Coarse, dry hair and dry skin
- Hair loss
- Sensitivity to cold
- Muscle cramps and aches
- Constipation
- Depression
- Irritability
- Memory loss
- Abnormal menstrual cycles
- Decreased libido

SYMPTOMS OF LOW TESTOSTERONE
- Decreased sex drive (libido)
- Poor (or no) erections (erectile dysfunction or impotence)
- Enlarged breasts
- Mood swings (including increased irritability)
- Depression
- Hot flashes
- Change in sleep patterns
- Decreased strength
- Fatigue
- Weight gain

CAUSES OF GHD IN ADULTS
- Trauma
- Aneurysm
- Central nervous system infection
- Tumors of hypothalamus or pituitary
  - Pituitary adenomas
  - Craniopharyngioma
  - Brain abscess
  - Cysts
  - Metastases
  - Infections
- Infiltrative/ granulomatous disease
  - Langerhans cell histiocytosis
  - Sarcoïdosis
  - Tuberculosis
  - Hyperparathyroidism
  - Other
- Cranial irradiation
- Surgery of the pituitary or hypothalamus
- Infarction
  - Stroke
  - Abscess or a tumor
Regulation of GH Secretion

- Stimulators: GHRH, starvation, hypoglycemia, exercise, stress, deep sleep, ghrelin
- Inhibitors: somatostatin, obesity, aging, hyperglycemia, somatomedins

EVALUATION OF HYPOPITUITARISM

- 2005 consensus guidelines: screen all moderate and severe or any with symptoms suggestive of hypopituitarism
- Morning cortisol, FT3, FT4, TSH, IGF-1, FSH, LH, testosterone (males), estradiol (females), prolactin, and a 24 h urine collection for urinary free cortisol
- Provocative testing if symptoms and IGF-1 are suggestive:
  - Insulin (gold standard), glucagon. GHRH (no longer available), arginine, clonidine, L-dopa are used to stimulate peak GH
  - Deficient <6 ng/dl; severe deficiency <3 ng/dl
  - Insulin-Contra-indications include age over 60 years, coronary heart disease, epilepsy, untreated hypothyroidism, severe panhypopituitarism and hypoadrenalism

GROWTH HORMONE REPLACEMENT THERAPY

- Daily subcutaneous injection of recombinant human growth hormone (rhGH)
- Injection is into lower abdomen adipose tissue
- Range is typically 0.2 mg to 1.0 mg daily, adjusted according to therapeutic response, IGF-1 level and adverse effects.
- Four studies reported treatment effects in GHD caused by TBI:
  - High, 2010: Reimunde, 2011; Moreau, 2013; Devesa, 2013

HIGH, 2010

- 83 moderate to severe TBI
- 43/83 (52%) with GHD (<3 mg/ml)
- 23/43 participated
- Double-blind, placebo-controlled design: 12 GH/11 placebo
- GH titrated to IGF-1 in upper half of normal
- Improved: motor speed, information-processing speed, executive functioning, and memory.
- First double blind placebo controlled study of TBI.


**Former NFL Players—Pilot Study**

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<thead>
<tr>
<th>Patient</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
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<tbody>
<tr>
<td>Quality of Life (QoL)</td>
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<tr>
<td>Severe dissociative symptoms</td>
<td>0.6</td>
<td>0.6</td>
<td>0.4</td>
<td>0.4</td>
<td>0.6</td>
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<tr>
<td>Cognitive function</td>
<td>6.5</td>
<td>4.5</td>
<td>3.5</td>
<td>2.5</td>
<td>1.5</td>
<td>0.5</td>
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<tr>
<td>Emotional well-being</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7</td>
<td>0.6</td>
<td>0.5</td>
<td>0.4</td>
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<tr>
<td>Social functioning</td>
<td>9.2</td>
<td>8.2</td>
<td>7.2</td>
<td>6.2</td>
<td>5.2</td>
<td>4.2</td>
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**Quality of Life**

- Had GH level < 0.1 ng/ml
- After 1 yr of GHRT:
  - In college now
  - Mom: “I got my kid back”
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<th>CONCLUSIONS</th>
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<td>- Hypopituitarism has symptoms which are mistaken for TBI symptoms</td>
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<td>- Still undiagnosed in TBI</td>
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<td>- Is a treatable complication of head/brain injury</td>
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<td>- Quality of life, cognition, psychiatric symptoms, possibly mortality responsive to treatment</td>
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<td>- Screening in moderate and severe or mild if symptoms suggestive</td>
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<td>- Requires provocative testing to determine peak level of cortisol and growth hormone.</td>
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<td>- Lifelong replacement at a cost of $20,000/yr (damages)</td>
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