Traumatic Brain Injury – Post-Traumatic Hypopituitarism

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THE Transitional Learning Center
AT GALVESTON

Specializing solely in post-acute brain injury rehab since 1982
Pioneering Miracles
Institute of Medicine:

“…that hormonal alterations substantially modify the posttraumatic clinical course and the success of therapy and rehabilitation underscores the need for the identification and appropriate timely management of hormone deficiencies to optimize patient recovery from head trauma, to improve quality of life and to avoid the long term adverse consequences of untreated hypopituitarism”

IOM  Gulf War and Health, 2009
Traumatic Brain Injury and Hypopituitarism

- Describe the function and anatomy of the pituitary gland
- Increase awareness of hypopituitarism
- Describe the signs and symptoms of hypopituitarism
- Describe screening and treatment options for hypopituitarism
Where is the Pituitary Gland?
What Is the Function of the Pituitary Gland?
Feedback Loop

Hypothalamus

Pituitary

Trophic Hormone

(+)

Target Endocrine Organ

(-)

Target Hormone
Normal Anterior Pituitary Hormonal Function Essential for Maximizing Rehabilitation

- **TSH**
  - Thyroxine
    - Memory
    - Mood
    - Metabolism
    - Energy
    - Neuromuscular

- **ACTH**
  - Cortisol
    - Mood
    - Electrolytes
    - Energy
    - Stress

- **FSH**
  - LH
  - Testosterone
    - Estrogen
    - Energy
    - Mood
    - Libido
    - Reproduction
    - Muscle mass

- **GH**
  - IGF-I
  - Muscle mass
  - Energy
  - Exercise capacity
Pathophysiology of Hypothalamic-Pituitary Vulnerability

- **Sites of injury**
  - Hypothalamus
  - Stalk
  - Pituitary gland

- **Types of injury**
  - Direct trauma
  - Vascular insults
    - Brain swelling / ICP
    - Vasospasm
    - Hemorrhage
    - Hypotension / hypoxia
    - Pituitary swelling
    - Infarction
    - Ischemia

<table>
<thead>
<tr>
<th></th>
<th>Incidence of PTH</th>
<th>17 studies - Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>809 Chronic TBI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>8-36%</td>
<td></td>
</tr>
<tr>
<td>LH/FSH</td>
<td>0-17.1%</td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>0-19.2%</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>1-10%</td>
<td></td>
</tr>
<tr>
<td>Hypopit</td>
<td>22-50%</td>
<td></td>
</tr>
<tr>
<td><strong>102 Chronic SAH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>12-36%</td>
<td></td>
</tr>
<tr>
<td>LH/FSH</td>
<td>0-13%</td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>6-40%</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>1.5-9.4%</td>
<td></td>
</tr>
<tr>
<td>Hypopit</td>
<td>27-55%</td>
<td></td>
</tr>
</tbody>
</table>

Schneider et al, JAMA, 2007;(298)12
Percentage of Single Pituitary Deficits Three Months after TBI or SAH

Percentage of Single Pituitary Deficits 12 Months after TBI or SAH

Pituitary Function in 50 Adult Patients with TBI over 5 Years

- Normal pituitary function (46%, n=23)
- Severe GHD (23%, n=13)
- Partial GHD (16%, n=8)
- Partial GHD + other (8%, n=4)

Some form of GHD (28%, n=14)


GHRH + ARG test
Partial GHD defined as:
• GH peak 9 µg/L to 16.5 µg/L
Severe GHD defined as:
• GH peak <9 µg/L
Difficult to Predict the Degree of Pituitary Dysfunction Following TBI/SAH

Patients at highest risk appear to be those who have suffered moderate-to-severe head trauma.

However:
In patients with moderate-to-severe injuries, no correlation has been observed among the site of trauma, severity of cerebral injury, and the degree of impairment of pituitary dysfunction.

No studies on mild TBI

Symptoms of Hypopituitarism Often Mimic Sequelae of TBI or SAH

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Symptoms of Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH</td>
<td>Abnormal body composition (decreased lean body mass, increased abdominal adiposity, dyslipidemia, reduced strength and exercise capacity, impaired psychological well-being, fatigue, osteoporosis</td>
</tr>
<tr>
<td>TSH</td>
<td>Fatigue, myopathy, weakness, decreased cognitive function, decreased libido, depression, irritability, menstrual irregularity</td>
</tr>
<tr>
<td>ACTH / cortisol</td>
<td>Hypotension, fatigue, weakness, weight loss, anorexia, inability to respond to stress, mood disorders, decreased memory</td>
</tr>
<tr>
<td>FSH / LH</td>
<td>Menstrual irregularity, decreased libido, impotence, infertility, decreased bone/muscle mass, fatigue, depression</td>
</tr>
<tr>
<td>ADH</td>
<td>Dehydration, polyuria</td>
</tr>
</tbody>
</table>

Elovic E. *J Head Trauma Rehabil.* 2003;18:541-543.
Thyroid Dysfunction

Hypothyroidism in ~5% mod-severe >1yr post TBI

- weight gain
- shortness of breath
- intellectual impairment
- cardiovascular disease

Agha Clin Endo, 2006
Gonadal Hormone Dysfunction

- 10-15% >1 year post mod-severe TBI
- 40-60% of individuals complain of sexual dysfunction post TBI
  males: decreased libido
decreased muscle mass
decreased strength

----correlation between low free testosterone and cognitive function

Zasler, Brain Injury Medicine, 2007
Agha, Clin Endo, 2006
Tan, Arch Intern Med, 2008
Overlap of Symptoms

Post-concussion Syndrome
- Headache
- Dizziness
- Blurred vision
- Sleep disturbance
- Sensitivity to light/noise
- Balance problems
- Memory deficits
- Slowed processing
- Impaired judgment
- Altered executive function
- Agitation
- Irritability
- Impulsivity
- Aggression

Fatigue
- Poor memory
- Anxiety
- Weight gain/weight loss
- Emotional lability
- Lack of concentration
- Attention difficulties

NED
- Loss of libido
- Infertility
- Amenorrhea
- Loss of muscle mass
- Increased belly body fat
- Low blood pressure
- Reduced heart rate
- Hair loss
- Anemia
- Constipation
- Cold intolerance
- Dry skin
Physical Functioning in TBI

- Norm—TBI subjects with normal GH levels
- GHI—Growth hormone insufficient (GH 4-8)
- GHD—Growth hormone deficient (GH<4)

<table>
<thead>
<tr>
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<th>Placebo (%)</th>
<th>GH (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>More alert</td>
<td>0.0</td>
<td>69.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Greater endurance</td>
<td>3.6</td>
<td>60.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>More active</td>
<td>3.7</td>
<td>51.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>More industrious</td>
<td>3.3</td>
<td>46.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>More extroverted</td>
<td>3.4</td>
<td>37.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Happier</td>
<td>11.1</td>
<td>48.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Better looks</td>
<td>10.3</td>
<td>51.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Better personal relationships</td>
<td>3.4</td>
<td>34.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>More satisfied with occupation</td>
<td>7.7</td>
<td>34.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Less worried</td>
<td>6.9</td>
<td>37.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Less easily annoyed</td>
<td>7.1</td>
<td>28.6</td>
<td>NS</td>
</tr>
<tr>
<td>Fewer family conflicts</td>
<td>3.4</td>
<td>24.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

GH Treatment: Outcomes

- Improved lipid profile
- Improved bone density
- Increased muscle mass
- Enhanced exercise tolerance
- Improved sense of well-being and quality of life
- Reduced body fat

GH Therapy: Adverse Events

Usually self-limited, dose related
– Swelling, inflammation in periphery
– Arthralgia, myalgia
– Pain or stiffness in extremities
– Paresthesias
– Increased glucose resistance/rarely type 2 diabetes

Can ONLY be given by injection

Pediatric TBI

- >30,000 children disabled annually from TBI
- Children with TBIs grow up to be adults with TBIs
- Incidence of hypopit in Pedi TBI: 0% to 35%

CDC, 2007
Heather, JCEM, 2012
Aimaretti, JCEM, 2005
Pediatric TBI

- Intact hypothalamic-pituitary axis needed for:
  - Proper development and growth
  - Physical and emotional maturation
- Deficiencies result: short stature, hypogonadism, arrested puberty, precocious puberty, cognitive deficits.
Precocious Puberty

- Pediatric TBI: Precocious puberty induces early bone maturation: short females at risk for sexual abuse and greater risk for breast cancer
- Males: aggressiveness
Mild TBI and Pituitary Dysfunction

- Study assessed 33 subjects with mild TBI available with an age of 31+/- 10 years.
- The ethnic composition showed 33.3% Caucasians, 30.7% Latino, 30.7% African Americans, and 5.1% Asian.
- Blood was drawn for assessment of pituitary function on 33 of the 39 subjects at 6 months post mTBI.
- Of the 33 subjects, 23 were males (69.7%) and 10 were females (30.3%).
- The vast majority of injuries resulted from either a motor vehicle accident, fall, or an assault.
Mild TBI and Pituitary Dysfunction

- 28 subjects had IGF-1 levels measured
  - 53.5% (15/28) IGF-I < 175 ng/ml
  - 35.7% (10/28) male
  - 17.85% (5/28) female
- 23% of males had a low total testosterone
- Thyroid and cortisol levels were in the normal range
Mild TBI and Pituitary Dysfunction

- IGF-1 (ng/ml) levels were significantly associated with total recall on a verbal learning measure ($r=0.47$, $p=0.029$) at 6 months.

- IGF-1 (ng/ml) levels were significantly associated with a measure of TBI symptom endorsement ($r=-0.64$, $p=0.014$) at 6 months.
Cognitive Complaints in GH Deficient mTBI Patients

• “Foggy brain”
• Short term memory loss
• Slow response to conversations
• Can’t organize their day - survive by making lists
• Many can no longer maintain their jobs
Fatigue in GH Deficient TBI Patients

• Profound
• Increased sleepiness, yet with disturbance in sleep
• No longer able to maintain their usual activity levels
• Other hormone replacements do not improve
• With rhGH replacement, fatigue symptoms often improve within 3 months
Hypopit and NFL football

- 68 retired NFL players >5yrs career
- Median concussions = 3
- 23% had hormonal deficits
  - 15% GHD
  - 4.4% Hypogonadal
  - 4.4% Both

Kelly et al, J Neurotrauma, 2014
Hypopit and NFL

• In retired players complaining of poor Quality of Life:
  • 19% had GHD
  • 9% had Hypogonadism
  • 59% had metabolic syndrome (increased abdominal fat, insulin resistance, dyslipidemia, hypertension)
When Should Patients be Screened?

All TBI Patients (regardless of severity)
- First visit during hospitalization in Neurosurgery or ICU: Conduct hormonal testing if clinically indicated
- 3-month evaluation: Conduct baseline hormonal work-up
- 12-month evaluation: Conduct baseline hormonal work-up

Patients with Moderate or Severe TBI >12 months prior
- First visit: Record a detailed patient and family history
- Conduct baseline: hormonal work-up in a single session

Screening that can be ordered by any physician

Thyroid:  TSH, Free T4
Adrenals:  Morning cortisol
Prolactin secretion:  Serum prolactin
Females:  Menstrual history or 17 beta estradiol
Males:  Total serum testosterone
GH:  IGF-1

Note if the IGF-1 level is less than 175----should be referred to Endocrinologist for provocative testing  
Zgaljardic et al, Clin Endo 2011
Screening Performed by an Endocrinologist

- ACTH secretion: Low dose (1mcg) IVP cosyntropin stimulation test
- GH secretion: GH stimulation test
Hormone Replacement in Chronic TBI Subjects: Study Protocol

Chronic TBI subjects

- Screening - menstrual history, FSH, testosterone, free T4, TSH, prolactin, cosyntropin and glucagon stimulation test

- Normal, no further testing
- Thyroid abn LT4 - 6 m
- Cortisol abn Pred. - 6 m
- GH def rhGH - 1 y
<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>Placebo (n=11)</th>
<th>Active rhGH (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39.1 (8.5)</td>
<td>36.1 (10.0)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.1 (3.0)</td>
<td>14.8 (2.9)</td>
</tr>
<tr>
<td>Initial/lowest GCS Score</td>
<td>6.6 (3.6)</td>
<td>5.8 (3.4)</td>
</tr>
<tr>
<td>Baseline DRS score</td>
<td>3.1 (3.1)</td>
<td>2.3 (2.8)</td>
</tr>
<tr>
<td>Time since injury (yr)</td>
<td>5.1 (3.6)</td>
<td>11 (9.2)</td>
</tr>
</tbody>
</table>
rhGH Replacement in Moderate/Severe TBI Patients: Neuropsychological Testing

Finger Tapping - Dominant Hand
(covaried initial GH level)

* p=0.004 (1-tailed)

- Treatment, n=12
- Placebo, n=9

Significant interactions: Time x Group
* p=0.01 (1-tailed)
rhGH Replacement in Moderate/Severe TBI Patients: Neuropsychological Testing

WAIS-III: Processing Speed Index (PSI)
(covaried initial GH level)

* $p=0.01$ (1-tailed)

$\bullet$ Treatment, $n=11$

$\square$ Placebo, $n=10$

Significant Interactions:
Time x GH Level x Group
$*p=0.03$ (1-tailed)
rhGH Replacement in Moderate/Severe TBI Patients: Neuropsychological Testing

Wisconsin Card Sorting Test
(covaried initial GH level)

- Treatment, n=12
- Placebo, n=10

p=0.1 (1-tailed)

Significant Interactions:
Time x GH Level x Group
*p = 0.006
rhGH Replacement in Moderate/Severe TBI Patients: Neuropsychological Testing

California Verbal Learning Test - Trials 1-5 (covaried initial GH level)

* p=0.03 (1-tailed)

Main effect for Time (using Multivariate Test): Treatment Group Only
* p=.03 (1-tailed)
OXYGEN UPTAKE

Time (months)

VO$_2$ (mL/kg/min)

rhGH (n=10)

Placebo (n=11)
MINUTE VENTILATION

$V_E$ (L/min)

rhGH (n=10)
Placebo (n=11)
GH replacement--Neuropsychological testing results

- Improved processing speed
- Improved frontal lobe function
- Improved short term memory
- Improved dominant finger tapping speed

Single fiber muscle biopsy testing: baseline and 1 year

- Improvement in Type II (fast twitch) muscle power
- As force=power times velocity, and velocity did not change:
- Increase in Type II muscle power
- Placebo group had fiber atrophy/decreased power--rhGH group improved
GH replacement--Physical parameters results

- No significant differences in weights, fat or lean body mass
- Improved ventilatory exchange
- Improved oxygen uptake and minute ventilation
- Increased peak power of the Type II muscle fibers due to increase in force of contraction
Results Suggest:

Growth hormone replacement:
Improve physical functioning—exercise capacity
Improve some aspects of neurocognitive/neuropsychological functioning
(Studies like this are a whole lot of work)
Conclusions

• Hormonal deficiency occurs in 30% to 50% of patients who survive a moderate to severe TBI with GHD being the most common

• Hormonal deficiency after TBI could negatively affect quality of life, rehabilitation, and recovery

• Moderate to severe TBI patients should be screened for hypopituitarism

• Patients with mTBI and profound fatigue (>1 yr) should be screened for hypopit.
Thanks to my staff