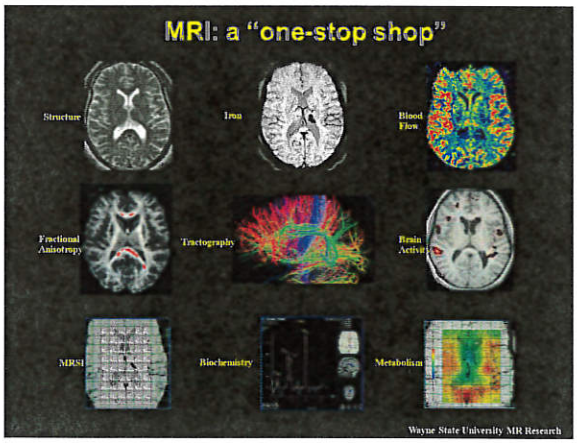
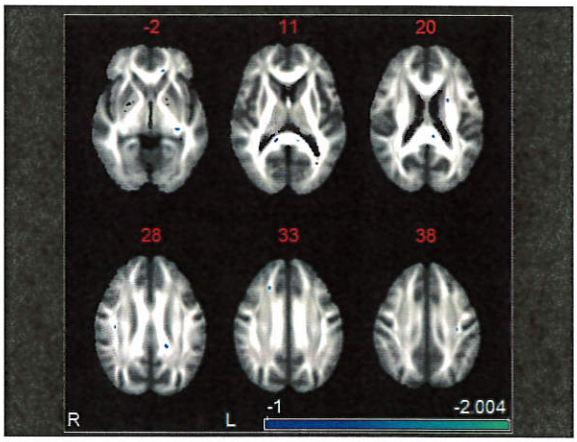
Pituitary Dysfunction after TBI

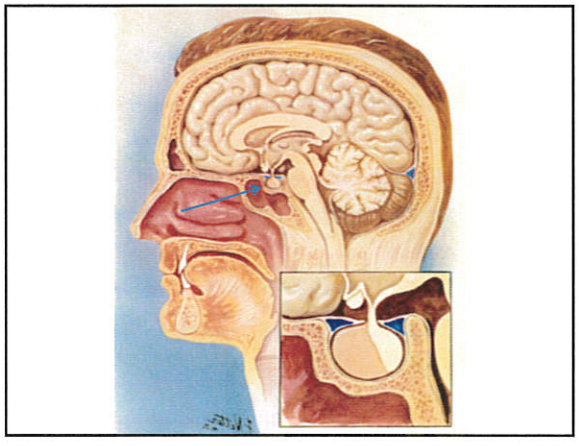
Randall Benson, M.D.
Center for Neurological Studies
Detroit, MI

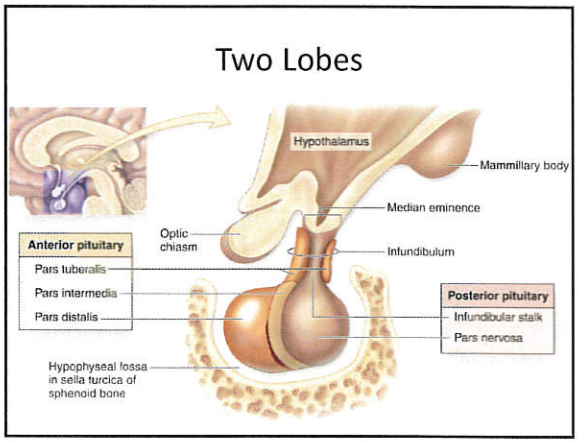


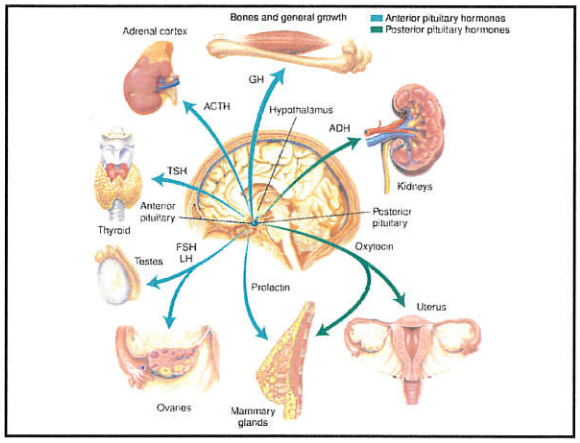
"PERSISTENT POSTCONCUSSIVE SYNDROME"

- 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!



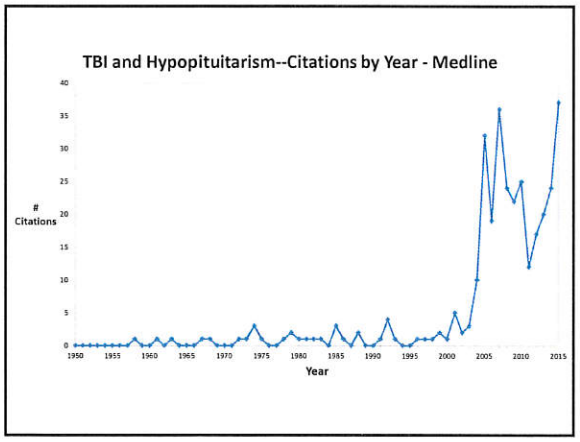






HISTORY OF TRAUMATIC HYPOPITUITARISM

- 1918--Case report in case of basilar skull fracture (German)
- 1942--Traumatic hypopit. reported in only 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.
- 2001--Post-traumatic endocrine deficits : analysis of a series of 93 severe traumatic brain injuries
- 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.
- **2011**--Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline



Reports of Deficiency by Hormone

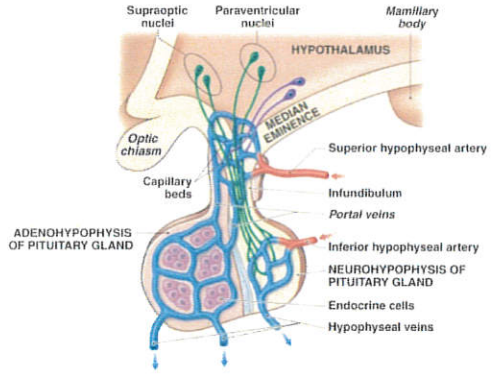
Study Design	Overall Rate	Adrenal	Thyroid	Prolactin	Gonadal	Growth Hormone	Antidiuretic Hormone
Prospective. 45 patients. Reported percent day1 day4 post TBI [21]	54%-70%	54%-70% (Serum cortisol 10 µg/dL)	Low fT4 5.5%-27.3% Low TSH 4.5%-15.9%	67%-77%	Females excluded. Low testosterone 52.1%-100% LH 55.2%-58.6% FSH 10.3%-17.9%	30.2%-32.3% (based on IGF-1)	No data
Prospective 50 patients median 12 days post TBI [16]	50%	16% (glucagon stimulation)	2% (fT4, TSH)	32%	80% (75% males low testosterone. 90% females low estradiol)	ITT 18% (peak GH 3 ng/mL) 16% (< 5 ng/mL)	26%
Prospective 78 patients, reported 3-12 months post TBI [23]	56%-58%	19%-9% (short ACTH stimulation)	9%-3% (T3 fT4, and TSH)	3%-4%	32%-21% (FSH, LH, testosterone and estradiol)	9%-10% (GHRH - Arg stimulation)	No data
Prospective 70 patients reported 3-12 months post TBI [24,42]	32.8%-22.7%	8.5%-7.1% (AM cortisol and 24 h urine cortisol)	7.2%-5.7% (T3 fT4, TSH)	4.2%-5.7%	17%-11.4% (FSH, LH, testosterone and estradiol)	21%-20% (GHRH - Arg stimulation)	9.2%-2.8%
Retrospective analysis of prospective database 192 TBI survivors median 17 months [13]	28.4%	12.7% (Glucagon stimulation or ITT)	0.95% (TSH, fT4: single patient with panhypopituitarism)	11.8%	11.8% (males only by testosterone and gonadotropin)	7.8% (by glucagon stimulation GHRH + Arg, or ITT)	No data

Reports of Deficiency by Hormone (cont'd)

Prospective. 70 patients median 13 months post TBI [24]	68.6%	45.7% (AM cortisol) 7.1% (Short ACTH stimulation)	21.7% with any abnormality (TSH 10%, fT4 8.6% and both 2.9%)	Increased in 6 males and 1 female (5 males and single female on PRL elevating drug)	None	14.6% (glucagon or L-DOPA stimulation)	No data
Retrospective and prospective 22 patients median of 26 months post TBI [24]	36.4%	None (ITT)	4.5% (TRH stimulation. TSH, fT4)	62%	22.2% males (GHRH. but all with normal testosterone). 25% females (GHRH. LH and estradiol)	18.2% (ITT)	No data

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. GHD and 2° hypogonadism 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



The Pituitary Gland and the Hypophyseal Portal System

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*
- *Lability (changes in mood)*
- *Depression*
- *Impairment of cognitive function*

SYMPTOMS OF LOW CORTISOL

- *Mental and psychological ailments such as depression*
- Faintness 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*

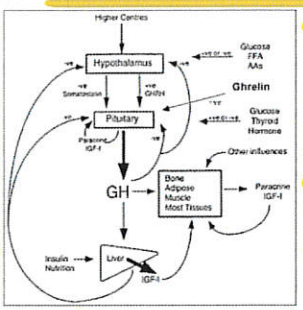
SYMPTOMS OF LOW TESTOSTERONE

- *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 adenoma
  - Craniopharyngioma
  - Rathke's cleft cyst
  - Glioma/astrocytoma
  - Germinoma
  - Metastatic
  - Other
- Infiltrative/granulomatous disease
  - Langerhans cell histiocytosis
  - Sarcoidosis
  - Tuberculosis
  - Hypophysitis
  - Other
- Cranial irradiation
- Surgery of the pituitary or hypothalamus
- Infarction
  - Spontaneous
  - Sheehan's syndrome

Regulation of GH Secretion



- **Stimulators**
  - **GHRH**
  - **starvations**
  - **hypoglycemia**
  - **exercise**
  - **stress**
  - **deep sleep**
  - **ghrelin**
- **Inhibitors**
  - **somatostatin**
  - **obesity**
  - **aging**
  - **hyperglycemia**
  - **somatomedins**

EVALUATION OF HYPOPITUITARISM

- 2005 consensus guidelines: screen all moderate and severes 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 <5 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 ng/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.

High, W.M., Jr., et al., *Effect of growth hormone replacement therapy on cognition after traumatic brain injury.* J Neurotrauma, 2010. 27(9): p. 1565-75.

REIMUNDE, 2011

- Subjects: 19 TBI with frontal contusions; 11/19 (58%) with GHD; 8/19 controls w/o GHD.
- Intervention: GHRT with cognitive rehab (active) vs. vehicle with cognitive rehab (controls) over 3 months.
- Results: GHD reached significantly greater improvements than controls for similarities ($p<0.01$) and in vocabulary, verbal IQ and total IQ ($p<0.05$).

Reimunde, P., et al., *Effects of growth hormone (GH) replacement and cognitive rehabilitation in patients with cognitive disorders after traumatic brain injury.* Brain Inj, 2011. 25(1): p. 65-73

MOREAU, 2013

- Aim: Effect on QoL, ADL, cognition in 50 symptomatic patients and 27 controls
- 28/50 (56%) with severe GHD, 15 with CD, 15 with TD
- Treat: Titrate GHRT to IGF-1 in upper half
- GHRT had a moderate effect on the speed of information processing and memory compared with controls.
- the patients with the greatest improvements were those who had the most severe difficulties before treatment;
- Improvements in QoL and ADL were related (at least in part) to the improvements in cognitive functions.

Moreau, O.K., et al., *Growth hormone replacement therapy in patients with traumatic brain injury.* J Neurotrauma, 2013. 30(11): p. 998-1006.

DEVESA, 2013

- GH with rehabilitation in severe TBI.
- 13 severe TBI.
- 5/13 showed GHD.
- Results:
  - For all patients (GHD and no-GHD), clear, significant improvement was observed.
  - Cognitive improvement appeared earlier and was greater than motor improvement.
  - Swallowing improved significantly in all 5 TBI patients with neurogenic dysphagia.
  - Visual function was improved in a patient with amaurosis.
  - No undesirable side-effects were observed.

Devesa, J., et al., *Growth hormone (GH) and brain trauma.* Horm Behav, 2013. **63**(2): p. 331-44

Falleti, M.G., et al., *The effects of growth hormone (GH) deficiency and GH replacement on cognitive performance in adults: a Meta-analysis of the current literature.* Psychoneuroendocrinology, 2006. **31**(6): p. 681-91.

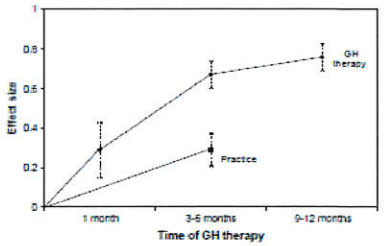


Figure 1 GH replacement therapy and its attention, memory, and executive function benefits after treatment (longitudinal studies).

Former NFL Players—Pilot Study

	Patient I	Patient II	Patient III	Patient IV	Patient V	Patient VI
Fasting Growth Hormone (ng/ml)	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1
GH Stim. Test Peak (ng/ml)	0.6	1	0.4	2	0.6	≤0.1
Fasting CBC (g/ml)	2.5	4	3.1	2.7	2.6	3
Free Cortisol Level (mg/dl)	0.97	0.49	0.29	0.24	0.67	0.83
Prolactin (ng/ml)	5.17	10.3	9.5	6.01	8.26	10.61
Free Testosterone (pg/ml)	9.2	6	7.7	9.8	5.6	12.2

Quality of Life

Quality of Life Assessment	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Fatigue						
Level of Energy	3 7 8	2 7 8 5	4 6 8 9–	2 4	3 6	3
Ability to Concentrate	2 8 7	1 1 3 7	5 6 8 9–	3 3	3 6	2
Anxiety	7 8	2 6	3 7	2 4	3 6	2
Agitation	3 8	1 6	2 8	2 4	3 6	2
Depression	3 5 6 8	1 6	4 7	2 6	4 6	2
Irritability	4 5 6 7	2 7	4 7	2 4	4 6	3
Aggression	4 7	4 6	5 7		4 5	2
Impaired Judgment	2 4 4 6	3 6	4 5 6 7-8	2 8	4 5	2
Slowed Processing	3 5 5 6	3 6		2 4	4 5	3
Impulsivity	3 8	3 6	5 6 6 7	2 3	4 6	2
Attention Difficulty	3 6	2 6	4 7	2 4	4 6	2
Emotional	2 4 7	2 6	5 7	3 4	4 6	2

Quality of Life are given a score of 1-10 (1 = poor, 10 = excellent).

Quality of Life

Sleep	2 8 8	3 7 7 9	3 8 9 10+	3 4	3 5	2
Strength	8 7 8	3 8 8	4 8	3 4	3 4	4
Memory (Short Term)	1-2 7 3	1 2 2	5 6 7 8	2 2	4 5	2
Others	3 3 8 8	1 4	5 6 7 7	2 2	3 6	4
Physical Endurance	3 7	4 6 9	4 7 8	4 6		
Pain Sensitivity	High Tolerance	High Tolerance	High Tolerance	High Tolerance	High Tolerance	High Tolerance
Frustration	3 7	2 4	4 7	3 4		
Symptom 21	2 6	1 5	2 6	2 6	3 7	2
Symptom 22	2 7	1 7	2 7	2 6	3 7	2
Light Sensitivity	4 7	2 4	4 6	3 6		2
Symptom 24	2 6	1 4	5 6	4 6	3 5	2
Taste	2 7	2 6	5 6	3	3 6	2
Smell	2 6	2 6		3 6	3 6	2
Balance	4 6	6 5	7 7	3 6	6 7	2

*Blue = Initial Visit *Red = Most Recent Visit

- Had GH level < 0.1 ng/ml
- After 1 yr of GHRT:
  - In college now
  - Mom: "I got my kid back"

CONCLUSIONS

- Hypopituitarism has symptoms which are mistaken for TBI symptoms
- Still underdiagnosed in TBI
- Is a treatable complication of head/brain injury
- Quality of life, cognition, psychiatric symptoms, possibly mortality responsive to treatment
- Screening in moderate and severe or mild if symptoms suggestive
- Requires provocative testing to determine peak level of cortisol and growth hormone.
- Lifelong replacement at a cost of $20,000/yr (damages)