Pituitary deficiencies after traumatic brain injury: Long-term impacts on health and recovery

Tamara L. Wexler, MD, PhD*

National Academics of Science, Engineering, and Medicine
Examining Traumatic Brain Injury as a Chronic Condition
March 11, 2025

Clinical Professor, NYU; Adjunct Professor, University of Pennsylvania

Pituitary deficiencies: Incidence and Time course

- **Pituitary deficiencies are seen at higher rates after TBI**
  - Chronic anterior pituitary deficiencies in 15-60% of adults after TBI
  - General population: < 0.05% prevalence
  - Pediatric rates at 1 year post-TBI range from 8-29%; with one report of 61% at 3yrs

  (Adults: Bondanelli 2004; Kreber 2016; Schneider 2006. Agha 2005; Izzo 2015; Silva 2015; Tsao 2010. Regal *et al* 2001. Pediatric: Kaulfers *et al* 2010, Krahulik *et al* 2017**,** Niederland *et al* 2007, Personnier *et al* 2014)

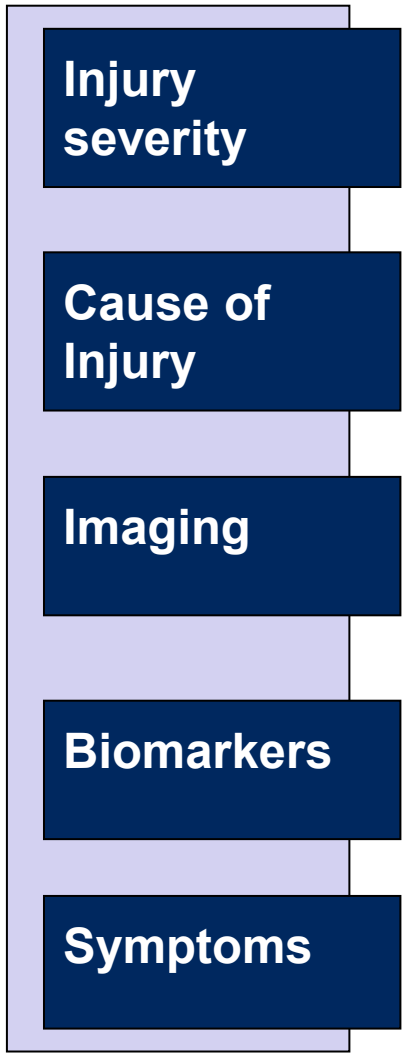
- **Deficiencies can develop after mild or severe TBI**

  (Aimaretti 2005, Tanriverdi 2015; Yuen 2022. Alavi 2016 ; Yang 2015)

- **Deficiencies may appear months (or years) after injury**
  - The same studies that describe recovery in some subjects find new deficiencies in others
  - New deficiencies, not present at 3 months, have appeared at 12 months in children and adults (Krahulik 2017; Casano-Sancho 2013; Aimaretti 2005) (Yang 2015)

- **Growth hormone (GH) and gonadal axes appear most commonly disrupted after TBI**
  - May vary with time since injury
  - Depends on diagnostic test and threshold employed

Pituitary deficiencies: Predictive characteristics



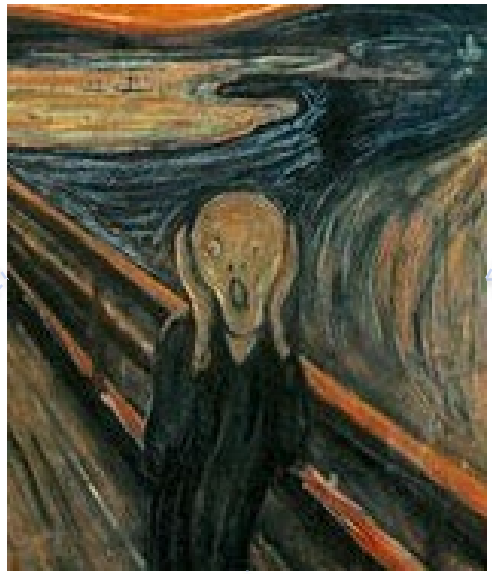
- Deficiencies can develop after mild concussions or severe TBI
- Deficiencies can develop after different causes of injury, based on studies of pituitary dysfunction after recurrent sports injury or military blast injury (Kelly et al 2014. Baxter *et al* 2013; Ciarlone 2020; Lee *et al* 2022; Undurti *et al* 2018)
- No clear correlation between imaging characteristics and incidence of pituitary dysfunction
- Anti-hypothalamus and anti-pituitary antibodies
  (60% and 48%, prospective study of 25 patients; at 5 years; Tanriverdi *et al* 2013)
- Symptoms of hypogonadism predict some type of pituitary dysfunction, but nonspecific symptoms do not (Cuesta *et al* 2016)

Pituitary deficiencies: Why do they matter?

Pituitary deficiencies impact health and quality of life (QOL) and, left untreated, are associated with increased mortality as well as morbidity

Changes to body composition, skin, hair

Skeletal and cardiovascular changes



Executive dysfunction, Mental fogginess

Fatigue, decreased exercise capacity

Irregular periods, decreased libido, sexual side effects

Mood changes, decreased quality of life

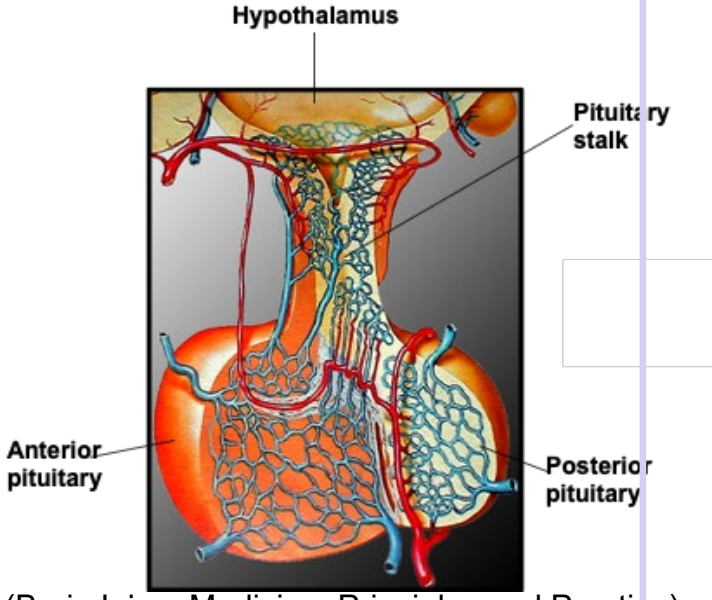
Pituitary and post-TBI symptoms overlap

The pituitary regulates various hormonal axes

- Anterior pituitary hormones:

GH	→	IGF-1
LH, FSH	→	estradiol in women; T, sperm in men
TSH	→	thyroid hormone
ACTH	→	cortisol
- - - - -		
PRL		

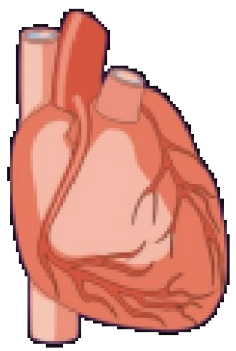
Tonic <u>inhibition</u> of PRL;
interruption may lead to elevation

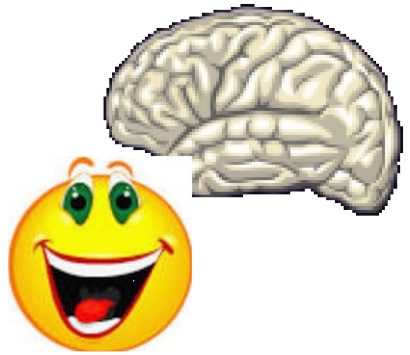


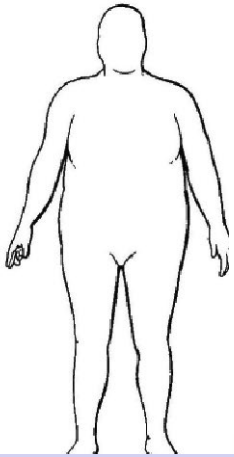
(Brain Injury Medicine: Principles and Practice)

GHD plays an important role in many areas – but may be overlooked in adults

- **Executive Function** (difficulties with cognitive processing, concentration, working memory)
- **Cardiovascular** (increased sbp, insulin resistance, dyslipidemia)
- **Bone** (low bone turnover)
- **Quality of Life**
- **Body composition** (increased visceral fat, decreased muscle)
- **Exercise capacity**







Implications of GHD after TBI

- GH acts throughout the body, negatively affecting quality of life, cognition, cardiovascular risk factors, bone strength, exercise capacity, and mood. Executive dysfunction– and decreased work productivity– are seen in adults with acquired GHD.
- GHD may contribute to QOL and neurocognitive sequelae after TBI. In studies of patients with TBI, those with GHD fare worse than those with sufficient GH (Kelly *et al* 2006; Kreber *et al* 2016)
- Improvements in cognition, quality of life, and body composition are reported with growth hormone replacement in patients with post-TBI GHD (High 2010, Gardner 2015; Tanriverdi 2010 and Bhagia 2010)

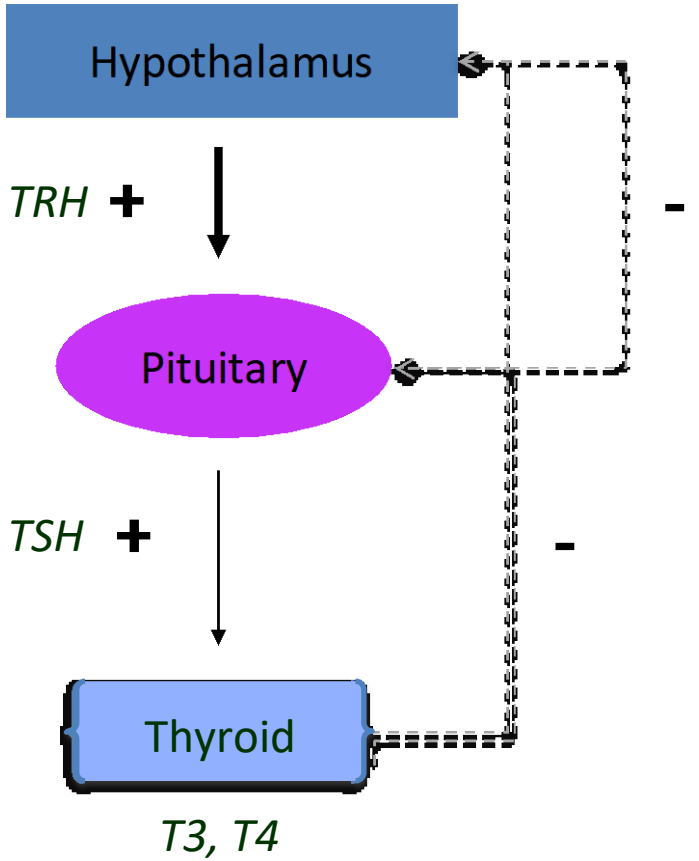
Why are post-TBI pituitary deficiencies missed?

- **Several factors contribute to underdiagnosis of pituitary deficiencies after TBI–missing the opportunity to reverse a contributor to chronic poor health**
  - Lack of awareness
  - “Vague” symptoms that overlap with symptoms due to other aspects of TBI
  - Incomplete understanding of patterns of pituitary (or hypothalamic) deficiency
  - Access to care and to tests used to diagnose pituitary hormone deficiencies

- **Common pitfalls provide a barrier to evaluation and treatment**
  - TSH alone cannot diagnose central hypothyroidism
  - Missed periods should not be assumed to be solely due to stress or menopause
  - Adult GHD may not be considered in patients after adult height is reached
  - IGF-1 may be inappropriately used as the sole test for GHD; evaluation most often requires provocative testing

Evaluation of pituitary axes: Principles

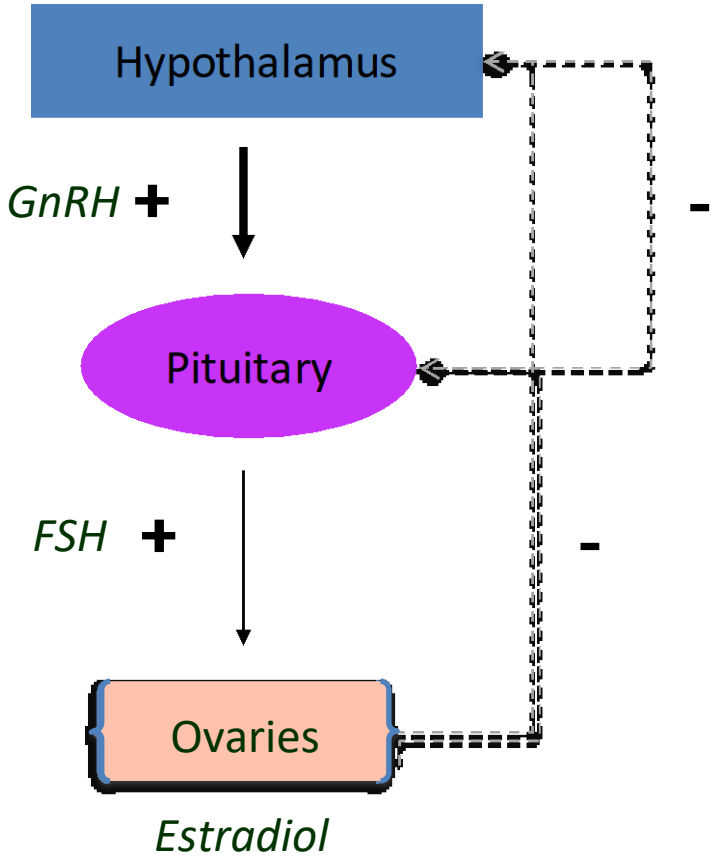
- **Context is essential** if anterior pituitary disease is suspected
  - "Normal" may be misleading
  - Time of day is important
  - Dynamic testing may be needed



A "normal" TSH in the presence of a low thyroid hormone level is inappropriately normal, and consistent with central hypothyroidism

Evaluation of pituitary axes: Principles

- Pituitary hypogonadism may masquerade as menopause
- Menstrual irregularities may indicate pituitary dysfunction
- Adolescents may present with delayed puberty



- high FSH suggests menopause
- low or inappropriately normal FSH suggests a central cause

Summary: Pituitary deficiencies after TBI

- **Pituitary dysfunction is an important sequela of TBI, one which can be diagnosed and treated.** Chronic deficiencies reported in 15-60% adults post-TBI
- **Hypopituitarism impacts health and quality of life and is associated with increased mortality as well as morbidity**
- **Pituitary axes should be evaluated in patients with signs or symptoms suggestive of dysfunction,** with a concussion or TBI history, given the reported incidence and the potential sequelae of deficiencies
- **Patients with hypopituitarism – diagnosed via appropriate testing -- should be offered replacement**; serial testing will identify those who have recovered, or new dysfunction. Symptoms due to pituitary dysfunction should be alleviated by replacement, but a return to overall baseline is not expected
- **There is ample opportunity for increased clinical awareness,** and, through research, answering outstanding questions regarding post-TBI pituitary deficiencies and their treatment

THANK YOU

Questions? Tamara.Wexler@nyulangone.org

References in main body only

- Aimaretti, G., Ambrosio, M. R., Di Somma, C., Gasperi, M., Cannavò, S., Scaroni, C., et al. (2005). Residual pituitary function after brain injury-induced hypopituitarism: a prospective 12-month study. *The Journal of Clinical Endocrinology and Metabolism*, *90*(11), 6085–6092. doi:10.1210/jc.2005-0504
- Alavi SA, Tan CL, Menon DK, Simpson HL, Hutchinson PJ. Incidence of pituitary dysfunction following traumatic brain injury: A prospective study from a regional neurosurgical centre. Br J Neurosurg. 2016 Jun;30(3):302-6. doi: 10.3109/02688697.2015.1109060. Epub 2015 Nov 26. PMID: 26610235.
- Baxter, D., Sharp, D. J., Feeney, C., Papadopoulou, D., Ham, T. E., Jilka, S., … Goldstone, A. P. (2013). Pituitary dysfunction after blast traumatic brain injury: The UK BIOSAP study. *Annals of Neurology*, *74*(4), 527–536. doi:10.1002/ana.23958
- Bhagia, V., Gilkison, C., Fitts, R. H., Zgaljardic, D. J., High, W. M., Jr, Masel, B. E., … Mossberg, K. A. (2010). Effect of recombinant growth hormone replacement in a growth hormone deficient subject recovering from mild traumatic brain injury: A case report. *Brain Injury*, *24*(3), 560–567. doi:10.3109/02699051003601705.
- Casano-Sancho, P., Suárez, L., Ibáñez, L., García-Fructuoso, G., Medina, J., & Febrer, A. (2013). Pituitary dysfunction after traumatic brain injury in children: is there a need for ongoing endocrine assessment? *Clinical Endocrinology*, *79*(6), 853–858. doi:10.1111/cen.12237
- Ciarlone, S. L., Statz, J. K., Goodrich, J. A., Norris, J. N., Goforth, C. W., Ahlers, S. T., & Tschiffely, A. E. (2020). Neuroendocrine function and associated mental health outcomes following mild traumatic brain injury in OEF-deployed service members. *Journal of Neuroscience Research*, *98*(6), 1174–1187. doi:10.1002/jnr.24604
- Cuesta, M., Hannon, M. J., Crowley, R. K., Behan, L. A., Tormey, W., Rawluk, D., … Thompson, C. J. (2016). Symptoms of gonadal dysfunction are more predictive of hypopituitarism than nonspecific symptoms in screening for pituitary dysfunction following moderate or severe traumatic brain injury. *Clinical Endocrinology*, *84*(1), 92–98. doi:10.1111/cen.12874
- Gardner, C. J., Mattsson, A. F., Daousi, C., Korbonits, M., Koltowska-Haggstrom, M., & Cuthbertson, D. J. (2015). GH deficiency after traumatic brain injury: improvement in quality of life with GH therapy: analysis of the KIMS database. *European Journal of Endocrinology*, *172*(4), 371–381. doi:10.1530/EJE-14-0654
- High, W. M., Jr, Briones-Galang, M., Clark, J. A., Gilkison, C., Mossberg, K. A., Zgaljardic, D. J., … Urban, R. J. (2010). Effect of growth hormone replacement therapy on cognition after traumatic brain injury. *Journal of Neurotrauma*, *27*(9), 1565–1575. doi:10.1089/neu.2009.1253
- Kelly, D. F., Chaloner, C., Evans, D., Mathews, A., Cohan, P., et al. (2014). Prevalence of pituitary hormone dysfunction, metabolic syndrome, and impaired quality of life in retired professional football players: a prospective study. *Journal of Neurotrauma*, *31*(13), 1161–1171. doi:10.1089/neu.2013.3212.

References (2)

- Krahulik, D., Aleksijevic, D., Smolka, V., Klaskova, E., et al. (2017). Prospective study of hypothalamo-hypophyseal dysfunction in children and adolescents following traumatic brain injury. *Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia*, *161*(1), 80–85. doi:10.5507/bp.2016.047
- Kreber, L. A., Griesbach, G. S., & Ashley, M. J. (2016). Detection of growth hormone deficiency in adults with chronic traumatic brain injury. *Journal of Neurotrauma*, *33*(17), 1607–1613. doi:10.1089/neu.2015.4127
- Leal-Cerro, A., Flores, J. M., & Rincon, M. (2005). Prevalence of hypopituitarism and growth hormone deficiency in adults long-term after severe traumatic brain injury. *Clin Endocrinol (Oxf)*, *62*(5), 525–532.
- Lithgow, K., Chin, A., Debert, C. T., & Kline, G. A. (2018). Utility of serum IGF-1 for diagnosis of growth hormone deficiency following traumatic brain injury and sport-related concussion. *BMC Endocrine Disorders*, *18*(1). doi:10.1186/s12902-018-0247-1
- Reifschneider, K., Auble, B. A., & Rose, S. R. (2015). Update of endocrine dysfunction following pediatric traumatic brain injury. *Journal of Clinical Medicine*, *4*(8), 1536–1560. doi:10.3390/jcm4081536
- Tanriverdi, F., Unluhizarci, K., Karaca, Z., Casanueva, F. F., & Kelestimur, F. (2010). Hypopituitarism due to sports related head trauma and the effects of growth hormone replacement in retired amateur boxers. *Pituitary*, *13*(2), 111–114. doi:10.1007/s11102-009-0204-0
- Tanriverdi, F., De Bellis, A., Ulutabanca, H., Bizzarro, A., Sinisi, A. A., Bellastella, G., et al.(2013). A five year prospective investigation of anterior pituitary function after traumatic brain injury: is hypopituitarism long-term after head trauma associated with autoimmunity? *Journal of Neurotrauma*, *30*(16), 1426–1433. doi:10.1089/neu.2012.2752
- Tanriverdi, F., & Kelestimur, F. (2015). Pituitary dysfunction following traumatic brain injury: clinical perspectives. *Neuropsychiatric Disease and Treatment*, *11*, 1835–1843. doi:10.2147/NDT.S65814
- Ulutabanca, H., Hatipoglu, N., Tanriverdi, F., Gökoglu, A., Keskin, M., Selcuklu, A., et al. (2014). Prospective investigation of anterior pituitary function in the acute phase and 12 months after pediatric traumatic brain injury. *Child's Nervous System: ChNS: Official Journal of the International Society for Pediatric Neurosurgery*, *30*(6), 1021–1028. doi:10.1007/s00381-013-2334-y
- Undurti, A., Colasurdo, E. A., Sikkema, C. L., Schultz, J. S., Peskind, E. R., Pagulayan, K. F., & Wilkinson, C. W. (2018). Chronic hypopituitarism associated with increased postconcussive symptoms is prevalent after blast-induced mild traumatic brain injury. *Frontiers in Neurology*, *9*. doi:10.3389/fneur.2018.00072
- Wexler TL, Neuroendocrine Dysfunction After Traumatic Brain Injury. In Zasler ND, Katz DI, Zafonte RD, Brain Injury Medicine, Third Edition (chapter 54). 2021. New York, NY: Demos Medical Publishing, Springer Publishing Company.

References (3)

- Wexler, T. L. (2023). Neuroendocrine disruptions following head injury. *Current Neurology and Neuroscience Reports*, *23*(5), 213–224. doi:10.1007/s11910-023-01263-5
- Yuen, K. C. J., Tritos, N. A., Samson, S. L., Hoffman, A. R., & Katznelson, L. (2016). American Association of Clinical Endocrinologists and American college of endocrinology disease state clinical review: Update on growth hormone stimulation testing and proposed revised cut-point for the glucagon stimulation test in the diagnosis of adult growth hormone deficiency. *Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*, *22*(10), 1235–1244. doi:10.4158/EP161407.DSCR
- Yang, A., Cho, S. Y., & Kwak, M. J. (2019). Impact of BMI on peak growth hormone responses to provocative tests and therapeutic outcome in children with growth hormone deficiency. *Sci Rep*, *9*(1).

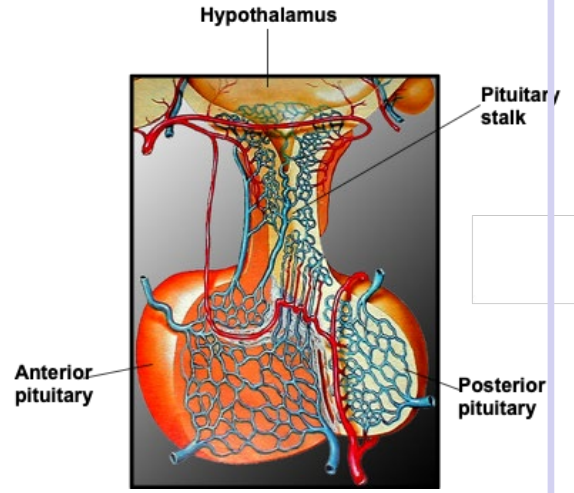
Appendix slides

The pituitary regulates various hormonal axes

- Anterior pituitary hormones:

GH	→	IGF-1
LH, FSH	→	estradiol in women; T, sperm in men
TSH	→	thyroid hormone
ACTH	→	cortisol
- - - - -		
PRL		

Tonic <u>inhibition</u> of PRL; interruption may lead to elevation



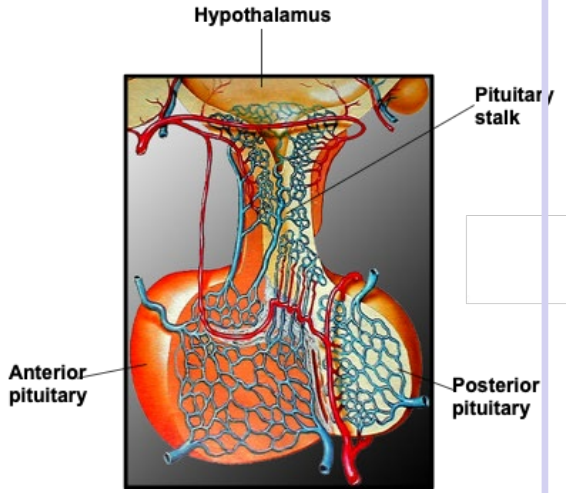
(Brain Injury Medicine: Principles and Practice)

The pituitary regulates various hormonal axes

- Anterior pituitary hormones:

GH	→	IGF-1
LH, FSH	→	estradiol in women; T, sperm in men
TSH	→	thyroid hormone
ACTH	→	cortisol
PRL		

Tonic <u>inhibition</u> of PRL; interruption may lead to elevation



(Brain Injury Medicine: Principles and Practice)

Symptoms of pituitary dysfunction

Symptoms may be broad, are often non-specific, and may include:

ACTH deficiency	▪ Mild fatigue to more severe nausea, weakness, weight loss, fever, confusion, hypotension ▪ Extreme stress can prompt (fatal) adrenal crisis
TSH deficiency	▪ Fatigue, weight gain, changes to hair and skin, constipation, cold intolerance, irregular menses ▪ Prepubertal: altered school performance
LH, FSH deficiency	▪ Women: irregular menses, dyspareunia, fatigue, mood changes ▪ Men: decreased libido, loss of spontaneous morning erections, depression, anemia, decreased body hair and muscle mass ▪ Prepubertal: delayed puberty
GH deficiency	▪ Decreased QOL, impaired executive function, increased visceral fat, reduced energy/exercise ▪ Prepubertal: impaired growth, altered fat distribution

Symptoms of pituitary dysfunction

- Prolactin can be either increased or decreased as a result of TBI

Prolactin

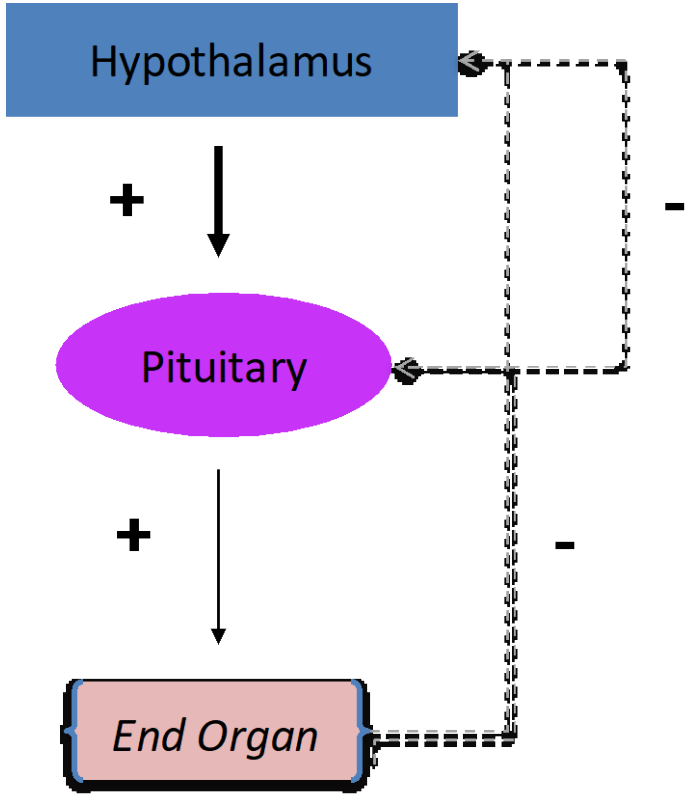
  - HyperPRL symptoms are from suppression of the gonadal axis; ~ galactorrhea (higher PRL)
  - HypoPRL: absence of lactation

***

- Pituitary dysfunction has physical, cognitive, and emotional sequelae
- Awareness of potential clinical presentations of pituitary dysfunction may help prompt needed evaluation
- **Following TBI, persistent symptoms suggestive of pituitary dysfunction should prompt consideration for full pituitary evaluation**

Evaluation of pituitary axes: Principles

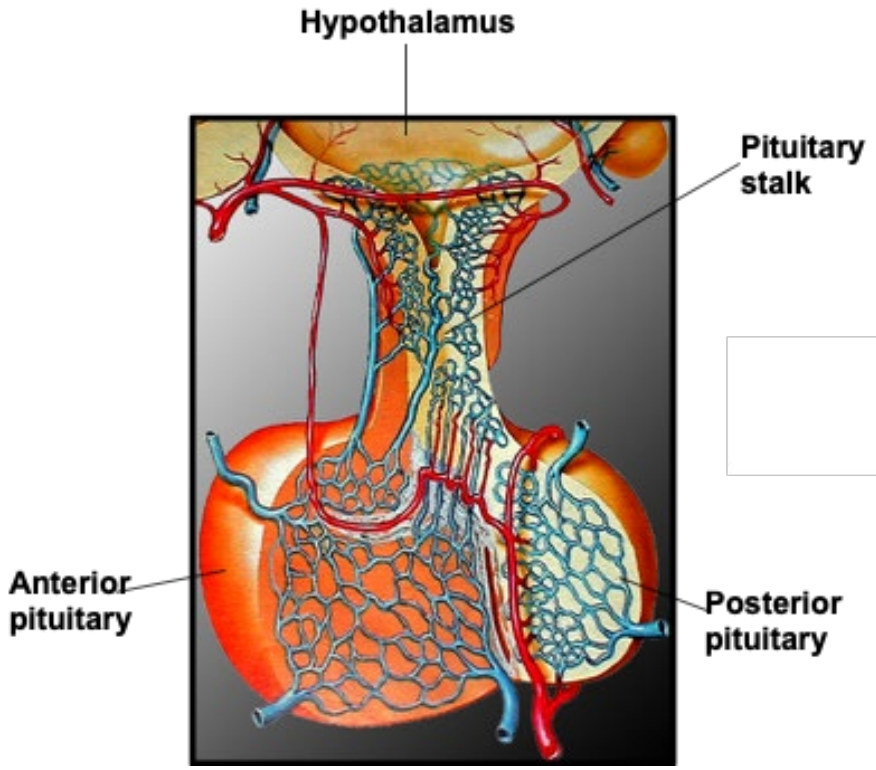
- **Context is essential** if anterior pituitary disease is suspected
  - "Normal" may be misleading
  - Time of day is important
  - Dynamic testing may be needed



Pituitary anatomy may predispose to injury

- Proposed models for pathogenesis include:
  - Primary injury from mechanical forces (vascular or axonal trauma from shear injury, or direct pituitary gland injury)
  - Ischemic injury from sequelae of the TBI (e.g., hypotension, hypoxia, or cerebral swelling)
  - Dysfunction from a secondary inflammatory state

- Anatomical location may confer vulnerability to mechanical forces or secondary ischemia
  - The pituitary sits within the bony sella turcica, its neurovascular stalk extending through the dura mater
  - Postmortem studies have found evidence of direct pituitary trauma after fatal TBI; no studies have correlated pathoanatomical findings with hypopituitarism
    (Aimaretti *et al* 2005; Salehi 2007)

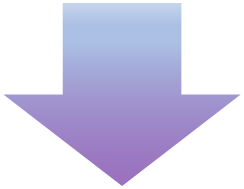


(Brain Injury Medicine: Principles and Practice)

Study variability promotes uncertainty

- **Variability in results may reflect different study designs, cohort features, and the way in which pituitary deficiencies are measured.** Growth hormone deficiency in particular has a wide range of methodology and definitions used across studies

- **Rate of pituitary dysfunction depends on a number of factors:**
  - At what time after injury are pituitary hormones measured?
  - Which patients are evaluated – what is the denominator?
  - What tests are used? Are guidelines followed?
  - What diagnostic thresholds are used?



Further carefully designed studies will help elucidate unanswered questions, determining whom and when to screen, and how to treat

Pituitary deficiencies: Practical guidelines

- **Replacement therapy is recommended for established pituitary deficiencies**
  - Replacement must proceed stepwise, with stabilization periods

    cortisol → thyroid → testosterone/estradiol → GH

  - Disruption in all axes is associated with morbidity: GHD is now the most commonly reported chronic post-TBI deficiency, and GH replacement has been associated with improved QOL and physical parameters; adrenal insufficiency can be fatal, and must be treated prior to thyroid hormone replacement
- **Symptoms due to pituitary dysfunction should be alleviated by replacement**, but a return to overall baseline is not expected
- **Evaluations may need to be repeated over time** (e.g., 6 months, 12 months, and yearly thereafter)

Pituitary deficiencies: Practical guidelines

- **Pituitary axes should be evaluated in patients with signs or symptoms suggestive of dysfunction,** with a concussion or TBI history, given the reported incidence and the potential sequelae of deficiencies

- **Referral to neuroendocrinology is recommended in the presence of persistent symptoms** such as irregular menses, decreased libido or spontaneous morning erections, fatigue and ‘mental fog,’ and new changes to weight/skin/hair.

- **Lab values may be useful for endocrine interpretation: early morning cortisol, TSH and free T4, LH/FSH/PRL and free T or E2 (unless normal menses), IGF-1**. Certain axes can’t be interpreted if other hormones are deficient. Interpretation and replacement should be referred to the endocrinologist; abnormal cortisol levels require immediate follow-up. Male hypogonadism cannot be diagnosed by a single morning value.

Testing for anterior pituitary deficiencies

Each axis is tested:

ACTH	▪ Insufficient peak cortisol to cosyntropin stimulation
TSH	▪ Low free T4 with inappropriately normal TSH
LH, FSH	▪ Men: 2 low morning T with inappropriately normal LH + symptoms ▪ Women: Irregular menses or inappropriately normal FSH
GH	▪ Low IGF-1 with 3 other deficiencies ▪ Insufficient peak GH on dynamic testing

Medications, herbs, and other remedies may impact hormonal levels

Testing for growth hormone deficiency

- The most appropriate (and available) test for GH sufficiency is not clear
- **Increasing evidence that IGF-1 is not a sufficient screening test for GH deficiency, except in the presence of 3 other deficiencies**
  - IGF-1 measurements can be normal in patients with GHD from TBI (Kreber 2016; Lithgow 2018)
  - No correlation between IGF-1 and peak GH on dynamic testing (Lithgow 2018: of 27 subjects with GHD--20 with peak GH <3--none had low IGF-1; Ulutabanca 2014: no pediatric correlation)
- Dynamic tests for adult GHD
  - Insulin tolerance test: "gold standard," but seizure risk
  - GHRH-arginine stimulation: not commercially available in U.S. (2008)
  - Glucagon stimulation test (GST)
  - Macimorelin (approved 12/20/17 for adult GHD)
  - Pediatric: clonidine, arginine

Testing access may be a barrier in some areas

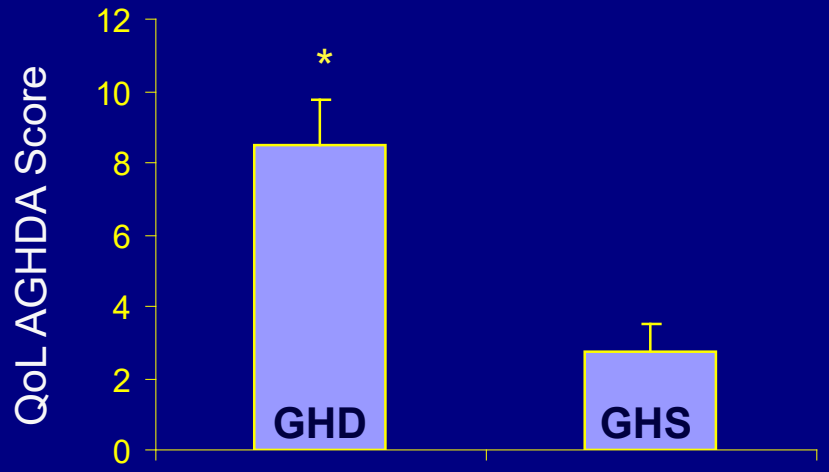
Defining growth hormone deficiency

- Per current guidelines for adults, a peak GH ≤ 3 mcg/L on glucagon stimulation testing is considered GHD, with potential BMI modifications
- Macimorelin is an oral ghrelin receptor agonist, with peak GH 2.8 mcg/L per FDA 2017 label, and 5.1 mcg/L per Phase 3 trial (Garcia *et al* 2018)
- Dynamic testing results appear affected by BMI in adults and children–even by relative abdominal adiposity in normal-BMI adults (Colao *et al* 2009; Deutschbein *et al* 2017; Qu *et al* 2005; Yang 2019)
- GHRH-arginine thresholds have been adjusted for BMI (Deutschbein *et al* 2017)
- Lower glucagon stimulation (GST) thresholds have been proposed
  - AACE/ACE guidelines suggest GST cutoff of 1 mcg/L peak GH in overweight, obese, or glucose-intolerant individuals (Yuen *et al* 2016)
  - One group suggests a 1.07 mcg/L GH peak cutoff on 4-hour GST, irrespective of BMI (Diri *et al* 2015--retrospective study of patients with pituitary disease)

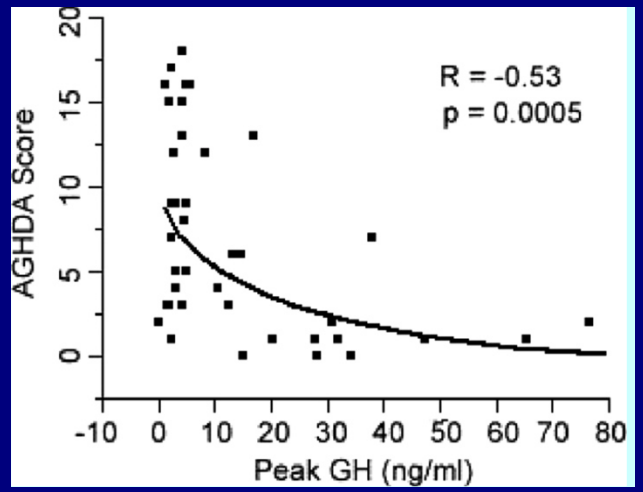
Pediatrics:
Traditionally, peak GH<10; better, assay-specific < -2 SD
More important: bone age and height velocity

QOL is impaired in GHD

- QOL Assessment of GH Deficiency in Adults (AGHDA) was compared with between post-acromegaly GHD and GH-sufficient patients
- Patients with GHD had similar degree of QOL impairment as in patients with GHD from other etiologies
- SF-36 showed similar results, and GHD patients had scores similar to those published for patients with type 2 diabetes and recent MI



GHD compared with GHS using QOL Assessment of GHD (AGHDA)



AGHDA score is inversely related to peak GH concentration

Wexler *et al* 2009