Brain Injury and Pituitary Dysfunction

Michael S. Sokol, MD
It has been estimated that approximately 1.7 million people with TBI are evaluated in United States hospitals annually, and approximately 52,000 patients die each year as a result of TBI.
The estimated burden of long-term disability related to TBI is even greater, affecting approximately 5.3 million individuals in the United States.
Furthermore, it is likely that TBI is underreported, particularly among patients with mild TBI or those with sports-related injuries, many of whom may suffer repeated head trauma.
Groups at high-risk for TBI include:
- males,
- young adults 15 to 24 years of age,
- children less than 5 years of age, and
- elderly persons over 75 years of age.
TBI severity, based on the Glasgow Coma Scale, is categorized as mild, moderate or severe. Some of the most common TBI causes are

- falls,
- unintentional blunt trauma,
- motor vehicle accidents,
- sports-related head trauma, and
- blast exposure.

According to data from the U.S. Centers for Disease Control and Prevention, there were over 2.2 million (715.7 per 100,000 population) TBI-related emergency room visits in 2010, and it is estimated that mTBI represents 70 to 90% of these cases. However, because a large number of concussions are not reported or treated, the incidence of mTBI is likely to be 2 to 5 times higher.

THEREFORE, traumatic brain injury is a major public health concern in the United States and other Western countries and accounts for substantial morbidity and mortality in both children and adults. There is evidence to suggest that TBI-induced hypopituitarism is common and is associated with substantial morbidity, increased mortality, as well as long-term disability in this population.
In the military, blast injuries have been recently recognized as a cause of TBI-associated hypopituitarism.
It has been known for over 100 years that brain injury may be associated with hypopituitarism, but recent evidence shows an even higher prevalence of anterior pituitary deficiencies than previously thought.
Although first reported in the literature in 1918, pituitary dysfunction after TBI garnered little attention from endocrinologists until the past decade or so.
Awareness of the problem of chronic hypopituitarism resulting from TBI has increased appreciably during the past 15 years. Studies during this period have reported a prevalence of chronic TBI-induced hypopituitarism ranging from 5 to 90%.

Approximately half of these studies reported frequencies of pituitary dysfunction between 25 and 50%.
6 studies of anterior pituitary dysfunction after repetitive concussion/mild TBI (mTBI) have been reported as a result of sports or military combat have reported a prevalence of 18-45%.

In a retrospective review of 166 adults with TBI, da Silva and colleagues found that certain injuries could be predictors of TBI-induced hypopituitarism. Their results demonstrated that patients who were involved in a motor vehicle accident as well as those with posttraumatic seizures, intracranial hemorrhage or petechial brain hemorrhage were at high risk for hypopituitarism.
Older patients and those who have suffered skull-base fractures or more severe TBI appear to be at higher risk of hypopituitarism.
Reports of pituitary deficiency in the acute period after injury are as high as 50% to 75%
Long-term survivors of both TBI and aneurysmal subarachnoid hemorrhage (SAH) have been found to have a 30-55% prevalence of at least one anterior pituitary deficiency when evaluated up to six years after the initial injury.
Hypopituitarism was associated with higher mortality in the intensive care unit (ICU) in this analysis.
In a systematic review of 14 studies reporting data on 1,014 patients, the prevalence of hypopituitarism was 35.3, 10.9, and 16.8% in patients with severe, moderate and mild TBI, respectively.
More consistent findings were reported in several recent studies regarding growth hormone deficiency and central hypothyroidism which occurred in approximately 25% and 5% of brain injury subjects respectively.
Hypopituitarism After Brain Injury: Summary of Recent Reports

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Number of Subjects (male/female)</th>
<th>Age of subjects (mean years)</th>
<th>TBI or SAH</th>
<th>Time since injury (mean months)</th>
<th>% At least 1 pituitary hormone deficiency</th>
<th>AI %</th>
<th>GHD %</th>
<th>HH %</th>
<th>CH %</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Kelly 2000 (2)</td>
<td>26 (18/8)</td>
<td>28</td>
<td>both</td>
<td>3</td>
<td>37</td>
<td>4</td>
<td>29</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Aimaretti 2004 (3)</td>
<td>100 (69/31)</td>
<td>37</td>
<td>TBI</td>
<td>3</td>
<td>35</td>
<td>8</td>
<td>25</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Aimaretti 2004 (3)</td>
<td>40 (14/26)</td>
<td>51</td>
<td>SAH</td>
<td>3</td>
<td>38</td>
<td>3</td>
<td>25</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>*Agha 2004 (4)</td>
<td>50 (38/12)</td>
<td>37</td>
<td>TBI</td>
<td>0.5</td>
<td>80</td>
<td>16</td>
<td>18</td>
<td>80†</td>
<td>2</td>
</tr>
<tr>
<td>Lieberman 2001 (8)</td>
<td>70 (46/24)</td>
<td>32</td>
<td>both</td>
<td>49</td>
<td>54</td>
<td>7</td>
<td>15</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Agha 2004 (7)</td>
<td>102 (85/17)</td>
<td>28</td>
<td>TBI</td>
<td>17</td>
<td>28</td>
<td>23</td>
<td>18</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Kreitschmann (6)</td>
<td>40 (14/26)</td>
<td>44</td>
<td>SAH</td>
<td>27</td>
<td>55</td>
<td>40</td>
<td>20</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Andermahr 2004</td>
<td>50 (40/10)</td>
<td>38</td>
<td>TBI</td>
<td>12 – 64 (range)</td>
<td>54</td>
<td>0</td>
<td>28</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

AI = adrenal insufficiency  GHD = growth hormone deficiency  HH = hypogonadotropic hypogonadism  CH = central hypothyroidism

*Indicates significant correlation between severity of injury and prevalence of pituitary hormone deficiency
SAH = subarachnoid hemorrhage  TBI = traumatic brain injury
both = subjects with SAH and TBI were included
† = this includes 50% of patients that had hyperprolactinemia as possible cause of HH

Lisa B. Nachtigall, MD; Brain Injury and pituitary Dysfunction. MGH Neuroendocrine Clinical Center Bulletin. Vol. 11, No. 2, 2005, pg. 2
Identification of patients with water imbalance is important because appropriate treatment may reduce morbidity and optimize the potential for recovery.
Disorders of water balance are well recognized after TBI, but there are limited reliable data on their true prevalence in post-TBI patients. In one study of 102 patients 21.6% developed diabetes insipidus (DI) in the immediate post-TBI period and permanent DI remained in 7% of patients.

Lisa B. Nachtigall, MD; Brain Injury and pituitary Dysfunction. MGH Neuroendocrine Clinical Center Bulletin. Vol. 11. No. 2, 2005, pg. 1
Central DI should be suspected in the presence of polyuria (urine output >200 mL/hour for at least 2 hours or 40 mL/kg/24 hours (>3 L/24 hours in patients of average weight) and/or hypernatremia. These patients are at risk for dehydration if their sensorium is clouded, they lack access to water, or suffer from hypodipsia or adipsia. The presence of DI has been associated with increased mortality in patients with moderate to severe TBI.
Pituitary imaging (magnetic resonance imaging [MRI]) generally reveals the absence of the “posterior bright spot” in unenhanced T1-weighted sequences in patients with central DI and may also show stalk disruption. Pituitary imaging additionally serves to exclude a nonadenomatous (or rarely, adenomatous) sellar mass as the cause of DI.
Central hypoadrenalism and diabetes insipidus (DI) may manifest in the acute phase after TBI, particularly in moderate and severe TBI, and should be considered early in the neuroendocrine evaluation of these patients. Up to 50% of hospitalized moderate or severe TBI patients may develop central hypoadrenalism, which can be associated with severe anemia, hypotension or hypoxia, as well as hyponatremia. Low serum cortisol levels have been associated with increased mortality in patients with moderate or severe TBI.
The symptoms and signs of hypopituitarism are not unique to pituitary dysfunction caused by TBI. Patients with central hypoadrenalism may also present more indolently with fatigue, weight loss, anorexia, dizziness, and joint aches several weeks or months after TBI. Although dynamic testing of pituitary adrenal function is not recommended during the acute phase after TBI, it can be helpful in establishing the diagnosis of central hypoadrenalism in stable patients several weeks after injury.
If the AM cortisol is less than 3 ug/dl, the diagnosis of adrenal insufficiency is established. If the AM cortisol is greater than 18 ug/dl (and perhaps as low as 14 ug/dL), then adrenal insufficiency is excluded in most patients. Levels of serum AM cortisol between 3 ug/dl and 18 ug/dl warrant a cortrosyn stimulation test, which should be done at least 6-12 weeks after the initial injury, as earlier testing may yield false negative results for central adrenal insufficiency.

Patients with central hypothyroidism are unlikely to present during the acute phase after TBI (owing to the long half-life of thyroxine). These patients may present with typical hypothyroid symptoms, including fatigue, weight gain, constipation, irregular menses, cold intolerance, neurocognitive dysfunction, depression, and hyponatremia, but notably lack of a goiter (in contrast with patients with Hashimoto’s disease).
The evaluation of the pituitary gonadal axis is appropriate only in stable outpatients during the rehabilitation phase after TBI, as acute illness or injury will generally result in suppression of gonadal function. Patients may present with sexual dysfunction, amenorrhea (women), and (occasionally) hot flashes.
Evaluation of the pituitary gonadal axis can be confounded by the suppressive effects of several medications, including opioids and glucocorticoids in pharmacologic doses. Hyperprolactinemia may also occur (in 11.8% of patients with TBI in one study) as a consequence of hypothalamic dysfunction, stalk interruption, and/or medication side effects and can be a contributing factor to the development of hypogonadism.

In patients with a past history of TBI, loss of secondary hair and bone mass may result. Of note, hypogonadal patients with a history of moderate to severe TBI appear to be less likely to gain functional independence during rehabilitation.

The patient would then require full testing for neuroendocrine dysfunction, which involves a typical pituitary panel: a thyroid function test, a thyroid-stimulating hormone and free thyroxine test, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), testosterone (in men), prolactin, adrenocorticotropic hormone and cortisol, GH and insulin-like growth factor.
It is not necessary to test menstruating women who are not on birth control, as regular menses are themselves an indication of an intact gonadal axis. Women who do not have regular periods should have their FSH, LH, estradiol and prolactin levels checked.
In men, it is best to check LH, FSH and testosterone. The diagnosis of low testosterone in men should be made only on the basis of early morning measurement; guidelines recommend two early morning measurements.
Randomly measured serum GH levels are of no diagnostic value in the assessment of GH secretion, as healthy adults have undetectable random GH levels during the daytime. Serum insulin-like growth factor 1 (IGF-1) levels lack sensitivity in the diagnosis of GH deficiency in adults.
Assessment of GH secretion should also be deferred for several months after TBI and should be conducted in patients whose other pituitary deficiencies have been replaced. Adult patients with GH deficiency may report poor stamina and exercise capacity, impaired quality of life, central adiposity and may develop dyslipidemia, insulin resistance, and low bone mass. Patients with TBI and GH deficiency may also report decreased memory and attention. Decreased linear growth is likely to occur in GH-deficient children or adolescents.

On the other hand, low serum IGF-1 levels can also be present in patients taking oral estrogen and those with liver disease or poorly controlled diabetes mellitus. However, patients with a known pituitary insult, low serum IGF-1 levels, and multiple (≥3) additional pituitary hormone deficiencies are very likely to be GH deficient (see Hartman M. et al. JCEM, 2004).

Dr. Randall Urban from UT Texas Galveston has found that the most common problem after TBI has been GH deficiency. These patients had a similar symptom complex. The first was profound fatigue.
Second, these patients experienced cognitive issues in three main areas:

- short-term memory,
- processing speed, and
- executive function.
Urban and colleagues have found that after 2 months of GH therapy, their patients’ fatigue began to decrease. At 4 to 5 months, their cognition began to improve. Usually, by a year, they’re going to be as good as they are going to be on this.
Urban and colleagues have been able to demonstrate that physical function, maximal oxygen consumption and fatigue improve with treatment. And some of these improvements have been dramatic, with patients returning to their jobs.
Some hormone issues appear immediately, whereas others develop with time. For instance, in the immediate aftermath of a TBI, a patient may develop
- adrenal insufficiency,
- diabetes insipidus and
- hyponatremia.
In time, problems such as
- hypothyroidism,
- hypogonadism and
- hyperprolactinemia may arise.
Adult patients seen in the acute phase after TBI may be re-evaluated at 2 to 6 months and 12 months. Recommendations regarding long-term retesting of pituitary function (>12 months after TBI) cannot be made in the absence of sufficient date.
Therefore, the most recent AACE Committee to address this problem recommends ongoing neuroendocrine surveillance at both 6 and 12 months after TBI to document resolution of temporary abnormalities and to ensure early intervention for persistent or late-occurring endocrinopathies in both children and adults.

Although the precise pathophysiology is still unknown, the current thinking is that during a TBI a direct mechanical injury or secondary insults – such as hypotension, hypoxia and brain swelling – damage the pituitary gland, leading to hormone deficiencies.
Several potential mechanisms have been proposed to explain the development of hypopituitarism in patients with TBI, including:

- Direct injury to the hypothalamo-hypophyseal unit and/or its blood supply,
- Compression of the pituitary as a result of edema,
- Hemorrhage or elevated intracranial pressure, and
- Trauma-related anemia, hypotensive and/or hypoxic insults.

The hypophyseal portal vessels passing through the diaphragma sella to supply the anterior pituitary are particularly susceptible to mechanical injury and compression, including those from

- direct shearing forces,
- local parasellar brain swelling and brain hemorrhage,
- raised intracranial pressure, and
- vasospasm.

However, more recently, diffusion tensor imaging revealed greater diffuse axonal injury (DAI) in the cerebellum and corpus callosum in TBI patients with pituitary dysfunction.

In another study, approximately one-third of TBI patients with DAI were found to have hypopituitarism, and these patients had more lesions in the body of the corpus callosum, basal ganglia, thalamus, and gray-white matter junction than those without hypopituitarism.
Research from Taheri and colleagues showed that circulating microRNAs may be potential biomarkers for TBI-induced pituitary dysfunction. The researchers studied microRNA expression in 38 patients in the acute phase of the study; in the chronic stage, they studied 25 patients who sustained a TBI 5 years earlier.
Research by Tanriverdi and colleagues found that autoimmunity may play a role in the development of post-TBI pituitary dysfunction. The researchers detected antipituitary antibodies in samples from 61 amateur boxers who were exposed to sports-related TBI.

Traumatic brain injury (TBI) is a significant health concern worldwide, resulting in 2.5 million ED visits, hospitalizations and deaths in the United States in 2010, according to the CDC.

In short-term studies approximately 35% of patients have at least one deficiency within three months of the initial injury.
Chronic pituitary deficiencies have been reported in 15% to more than 30% of patients after TBI.

Although it is clear that hormone replacement works – improving cognition, fatigue and quality of life – more research is needed. What hasn’t been done yet is any kind of intervention studies that show the change in either the rate of outcome or the ultimate recovery from TBI with hormonal therapy.
Many Thanks
In children, a recent prospective study evaluated pituitary dysfunction after TBI and found that the prevalence of neuroendocrine dysfunction was 15% at 1 month, 75% at 6 months, and 29% at 12 months. At one year after TBI, 14% had precocious puberty, 9% had hypothyroidism, and 5% had GH deficiency.
A study of 23 patients in the transition period (ages 16 to 25 years) found that hypopituitarism was present in 34.6% at 3 months after TBI, and at 12 months, hypopituitarism was present in 30.3%.

The Glasgow Coma Scale (GCS), consisting of additive ratings of motor response, verbal response, and eye opening within 24 hours of trauma, is almost universally used to rate TBI severity.

Charles W. Wilkinson, PhD; Commentary on a Neuroendocrine Approach to Patients with Traumatic Brain Injury. Endocrine Practice, Vol. 21, No. 7, 2015, pg. 851
The time between injury and GCS rating is highly variable, the individual components of the scale are seldom utilized, and cofounders are infrequently documented.
The use of pre-admission intubation and paralyzing or sedating agents also limit the accuracy of scores, the interobserver reliability is weak.
The CGS also fails to take into account the potential cumulative effects of repetitive injuries. These drawbacks complicate attempts at relating the occurrence of hypopituitarism to TBI severity.
It is often stated that (only) moderate and severe TBI are associated with hypopituitarism and that the frequency of occurrence of chronic hypopituitarism is related to the severity of the injury. However, definitive evidence for these suppositions is lacking.
The cumulative effect of sports-related head trauma on neuroendocrine function is supported by the significant relationships between the occurrence of hypopituitarism in boxers and the number of bouts fought and the age of retirement.

Charles W. Wilkinson, PhD; Commentary on a Neuroendocrine Approach to Patients with Traumatic Brain Injury. Endocrine Practice, Vol. 21, No. 7, 2015, pg. 851.
Current thinking about the potential mechanisms and loci of the pathophysiology of TBI-induced hypopituitarism has been reviewed by Dusick et al, but the factors involved are poorly understood. Tritos et al refer to preliminary studies associating PTHP with genetic factors linked to increased risk for Alzheimer’s disease as well as the possible involvement of antipituitary and antihypothalamic antibodies in its etiology. Although linkages between TBI and genetic risk factors for neurodegeneration and chronic traumatic encephalopathy are being investigated intensively, evidence for specific links of hypopituitarism to these factors is minimal. The autoimmune effects of TBI have been argued to be markers of pituitary damage as opposed to direct pathogenic mechanisms.

Early studies found enlarged pituitaries or focal hemorrhagic infarction in TBI patients, but pituitary volumes were not correlated with GCS scores or outcome ratings and/or neuroendocrine function was not tested.
Although there are few longitudinal studies of hypopituitarism after TBI. The consensus in the literature is that there is a high incidence of multiple endocrine abnormalities during the first few days after TBI, to the extent that 50-100% of patients present with endocrine deficiencies.
It is generally thought that during the succeeding months most deficiencies are normalized, whereas a smaller number of new deficiencies may appear. However, in 2 studies, a greater number of deficiencies were identified in the chronic phase after 5 or more months or 2 years post-TBI that in the acute phase.
Among 240 patients studied prospectively, there were 50 new hormone deficiencies and 113 recoveries of an endocrine axis by 12 months after TBI.

Morning serum cortisol levels ≤3 ug/dL are diagnostic of adrenal insufficiency. Patients with intermediate morning cortisol levels (3.1 to 17.9 ug/dL) may also have hypothalamic-pituitary-adrenal function in the chronic phase after TBI.
Among patients with hyponatremia who have not received diuretic or mannitol, the presence of inappropriately dilute urine (,700 mOsm/kg) is consistent with the diagnosis of DI. The water deprivation test can help establish the diagnosis of central DI and differentiate this condition from nephrogenic DI or primary polydipsia.
Patients with evidence of hypopituitarism should undergo pituitary imaging (MRI) to exclude the presence of a sellar mass.
According to Randall J. Urban, MD, in a subset of people, brain trauma – whether it is mild, moderate, severe or even repetitive – kicks off a chronic inflammatory process that leads to pituitary dysfunction.
There are several reasons for the fluctuating prevalence rates. The lack of a gold standard test for growth hormone deficiency and the confusion over what is a deficiency vs. suboptimal secretion make the prevalence data variable.
There are other cofounding factors. It depends on how the hormonal deficiency is assessed and the time post-injury as well as the severity of the injury as it relates to the TBI.
In addition, many of the medications that are given during the acute injury or later during the acute rehabilitation or chronic rehabilitation may impact hormone production.
There is no consensus on when to test patients with TBI for pituitary dysfunction, according to Endocrine Today Editorial Board member Lawrence Katznelson, MD, professor of neurosurgery and medicine and medical director of the pituitary at the Stanford University Medical Center.

Usually it’s found that although there can be some late comers when pituitary function seems to normalize, somewhere around 6 to 12 months after the event is when we should start the testing because for most patients, if they are pituitary deficient by then, they will remain pituitary deficient.
It would help to have a standardized way to describe concussions. – Tamara Wexler, MD, PhD
The literature suggests that the incidence is high immediately after injury.
If you look at the old literature . . . in the first 2 weeks after the injury, the incidence is way above 50%, maybe 70% to 100% of subhormonal abnormalities.
Then, it falls by 3 months. By 1 year, most of the hormonal abnormalities recover, although in some studies, new hormonal abnormalities occur. Some of these early studies were complicated by selection bias and inadequate testing criteria.
“There does appear to be a correlation with the development of [antipituitary and antihypothalamic] antibodies with subsequent hypopituitarism, although this is still not 100% correlation” – Laurence Katznelson, MD
In a more recently published systematic review of 66 studies (5,386 adult patients), the prevalence of persistent anterior pituitary hormone deficiencies was approximately 30%.

In the acute post-TBI period 13 patients (12.9%) had syndrome of inappropriate secretion of antidiuretic hormone, which persisted on one patient, and one other patient developed cerebral salt wasting.