

# NEUROENDOCRINE EFFECTS OF TRAUMATIC BRAIN INJURY

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## Key Points

- Neuroendocrine dysfunction after traumatic brain injury (TBI) is common, with an estimated prevalence of 25-30%. Given the frequency of TBI, even a lower prevalence would potentially constitute an important clinical problem.
- Vascular damage or direct trauma are likely primary causes of damage to pituitary and/or hypothalamus.
- Hypopituitarism is seen in the full range of TBI severities with somatotropin (GH) and gonadotropins (FSH,LH) being the most common deficiencies.
- Hypopituitarism post-TBI may impede rehabilitation and recovery. It has been associated with cognitive-behavioral deficits and reduced quality of life.

TBI is a common with the CDC reporting an estimated 1.7 million/yr. in 2010 and currently more than 2 million/yr. Although ~20-30% of TBIs are hospitalized and are more likely to be moderate or severe, the vast majority are of TBIs are mild. Current clinical classification of TBIs is as follows:

<b>Severity Grades of TBI</b>		
<b>Mild (Grade 1) "concussion"</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3 &amp; 4)</b>
LOC 0-30 min	LOC 30 min – 24 hrs	LOC ≥ 24 hrs
"Normal" CT/MRI	Abnormal CT/MRI	Abnormal CT/MRI
Glasgow Coma Scale 13 - 15	Glasgow Coma Scale 9 - 12	Glasgow Coma Scale < 9
Post-traumatic amnesia ≤ 24 hours	Post-traumatic amnesia 24 hrs - 7 days	Post-traumatic amnesia ≥ 7 days

Damage to the hypothalamic-pituitary system leading to neuroendocrine disorder after TBI is multi-factorial, but is thought to be primarily due to direct trauma to the long portal vessels leading to venous infarction of the pituitary. Post-mortem studies show a high prevalence of necrosis or hemorrhage into the pituitary. In addition, there are a variety of secondary insults that result from hypoxia, hypotension, increased intracranial pressure, etc. Clinically, hypopituitarism will present with signs of hormone deficiencies. For example, there may be a general sense of lack of well-being or change in body habitus. In children, loss of somatotropin or growth hormone (GH) will result in reduced growth velocity. The neurological manifestations of GH deficiency in adults are less clear, but data suggest that GH may influence cognition and behavior. Depending on the severity of the decrease in corticotropin (ACTH) and thyrotropin (TSH), patients may note lethargy, weakness, fatigability, cold intolerance, or constipation. Lack of gonadotropins (FSH, LH) may manifest with change in menstrual function, erectile dysfunction or decreased libido.

A systematic review of post-traumatic hypopituitarism by Schneider et al appeared in JAMA in 2007. They noted that while hypothalamo-pituitary dysfunction after TBI was first reported in 1918, it was considered rare. In their review of 809 cases of TBI, several months to 22 years post-injury, they found a hypopituitary prevalence rate of approximately 25%. Of particular interest was the occurrence of hypopituitarism across the spectrum of TBI severity, being observed in 16.9% of mild TBIs, 10.9% of moderate TBIs, and 35.3% of severe TBIs. In their series, hypogonadism and growth hormone deficiency were the most commonly observed problems. It was also noted that post-TBI hypopituitarism patients appeared to have poor quality of life, as well as abnormal body composition.

Although hypopituitarism is certainly an important issue in acute and subacute TBI, for neurologists practicing in an office setting, the presence of chronic neuroendocrine dysfunction is more likely to be of clinical interest. A subsequent study by the Schneider group (see Krewer et al), utilizing data from a large German database of hypopituitarism focused on hypopituitarism in the chronic phase of TBI, i.e. 1 to 5 years after injury. In this study of 245 TBI patients, it was found that the highest prevalence of neuroendocrine disorders was observed 1-2 years post-injury, tended to decrease over time, and then showed a second peak  $\geq 5$  years after injury. Gonadotropic and GH insufficiencies were most common, followed by ACTH and TSH insufficiency. In patients  $\geq 5$  years post-injury, the prevalence of growth hormone insufficiency reached 24.1% (ACTH and TSH insufficiency declined). However, due to differences in diagnostic criteria and diagnostic methodologies, there remains controversy about the true prevalence of hypopituitarism after TBI and guidelines for assessment of neuroendocrine function.

The Krewer study also examined neuroendocrine dysfunction after subarachnoid hemorrhage. They reported on the findings of basal hormonal levels in these patients, as well as TBI patients. Basal levels of hormones are easily obtained by most neurologists. In this group of 237 patients, a neuroendocrine disturbance was seen in 41 % (one axis – 36.7%, two axes - 7%, > 3 axes - 0.8%). Low testosterone was found in 14% of men, low estradiol in 10.8% of women, low IGF-1 (a marker of growth hormone) in 13.8%, and lowered cortisol or thyroxine in 7.2% and 3.3% respectively. Interestingly, in some patients elevated basal hormone levels were observed, notably in cortisol.

### **Who should be screened and treated?**

TBI is common, thus abnormal endocrine function in even a small percentage of patients, would have relevance to a substantial number of individuals. However, the question arises as to who should be screened? It is generally agreed that all moderate TBIs and severe TBIs with good life expectancy and a reasonable quality of life should be considered for neuroendocrine evaluation. While abnormalities are observed in patients with or without symptoms, it is in individuals with symptoms, particularly symptoms of gonadal dysfunction, where abnormalities are most likely to be found. Hormone replacement should be offered in appropriate individuals. In adults with GH deficiency, neurological symptoms manifesting as cognitive-behavioral complaints may be subtle. It is in symptomatic patients, where GH deficiency is most often noted. Thus, neuroendocrine screening is not only recommended in moderate TBI and most severe TBI survivors, but should also be considered in patients with mild TBI and persistent complaints that are suggestive of hypopituitarism with any type of symptomatology.

A meta-analysis of the effects of GH deficiency in adults (not only with TBI) showed impairment in attention, memory, and executive functions when compared to matched controls. GH treatment improved with 3-6 months of GH treatment across multiple domains. GH has been shown to directly affect cognitive functioning by enhancing excitatory transmission through NMDA receptors and indirectly via IGF-1. In TBI, patients with severe GH deficiency and cognitive-behavioral dysfunction > 1 year post-TBI showed moderate improvement in memory and speed of processing after GH treatment. In a study examining longer term effects of GH replacement after TBI, benefits in quality of life were observed. Improvement in neuropsychological symptoms with GH replacement has also been observed in a cohort of military veterans experiencing severe blast TBIs with residual cognitive impairment.

### **How should neurologists approach evaluation of neuroendocrine dysfunction after TBI?**

A suggested scheme is as follows:

In mild TBI or concussion, most individuals should not be screened, however, those individuals with histories of abnormal imaging, cerebral edema, hypoxia, hypotension, increased intracranial pressure, prolonged intubation or hospitalization, or gonadal dysfunction should be screened. All moderate TBIs and severe TBIs with good life expectancy or reasonable quality of life should be screened. Screening should take place at approximately 1 or more years post-TBI.

The recommended screening labs should include 8 AM cortisol, LH, FSH, prolactin, IGF-1, TSH, Free T4 and 8 AM testosterone. It is important to remember that when evaluating GH, IGF-1 may not be sufficiently sensitive, and dynamic testing may be required in order to demonstrate a deficiency. Glucagon stimulation, which is relatively safe and easily performed, has been suggested as one reasonable testing method. If laboratory testing is abnormal or borderline with persistent symptoms, endocrine consultation should be obtained. On the other hand, if testing is normal, and there are persistent cognitive-behavioral symptoms with low clinical suspicion of a hormonal disorder, alternative diagnoses associated with TBI or other co-morbidities should be considered.

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