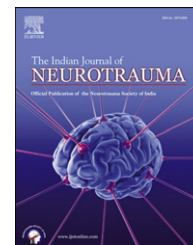


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## Review Article

## Endocrine manifestations of traumatic brain injury

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## ABSTRACT

Traumatic brain injury (TBI) is one of the causes of morbidity and mortality in young males, with consequences ranging from physical disabilities to cognitive, behavioral, psychological and social impairments. Traumatic brain injury (TBI) is a devastating public health problem and current data clearly establish that it may result in pituitary dysfunction in up to 20–50% have some degree of pituitary dysfunction after TBI. Although most cases of post-traumatic neuroendocrine dysfunction seem to be transient, persistent mild deficiency of pituitary hormones can be overlooked, as patients might have less-severe symptoms and their clinical course is often complicated by significant neurological disabilities. Presently there is paucity of prospective data on the natural history of post-traumatic neuroendocrine dysfunctions and there is need to develop appropriate guidelines for follow-up of suspected to have these dysfunctions so the information can lead to timely and appropriate assessment and treatment of hormonal deficits.

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## 1. Introduction

Traumatic brain injury (TBI) is one of the causes of morbidity and mortality in young males, with consequences ranging from physical impairment to long-term cognitive, behavioral, psychological and social impairments.<sup>1–4</sup> TBI is a devastating public health problem and current data clearly establish that it may result in pituitary dysfunction in up to 20–50% have some degree of pituitary dysfunction after TBI.<sup>5–9</sup> The first report of TBI – induced hypopituitarism was reported and published by Cyran in 1918 (almost a decade ago)<sup>10</sup> and since then hypopituitarism is increasingly recognized complication of brain injury.<sup>11</sup> The nonspecific symptoms may be masked by and may contribute to the physical and psychological

sequelae of brain trauma. This can explain why the diagnosis of hypopituitarism is often missed or delayed after these conditions – with potentially serious and sometimes life-threatening consequences for the affected patients. The purpose of this review is review the clinical and endocrinological manifestations on the occurrence of post-traumatic hypopituitarism (PTHP), and to identify the possible specific risk factors.

## 2. Epidemiology

TBI is a non-degenerative, non-congenital insult to the brain causing temporary or permanent neurological dysfunction

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resulting in impairment of endocrine, cognitive, physical and psychosocial functions.<sup>1</sup> The high incidence of TBI ranks it as potentially the most important cause of hypothalamic-pituitary dysfunction and different studies have estimated that 20–80% of patients who have suffered TBI will develop some degree of hypopituitarism.<sup>12–19</sup> Up to one-third of patients may be left with pituitary insufficiency; growth hormone deficiency as the most common deficits, followed by hypogonadism.<sup>20</sup> The pooled prevalence of hypopituitarism in the chronic phase after TBI and SAH was reported 27.5% and 47%, respectively.<sup>20</sup>

### 3. Risk factors

It is not well understood what factors predispose to development of post-traumatic hypopituitarism and several risk factors for the development of post-traumatic hypopituitarism have been identified and these include diffuse axonal injury, basal skull fracture and older age.<sup>21,22</sup> Severity of brain injury [particularly post-resuscitation Glasgow Coma Scale (GCS)<sup>23</sup>] has been shown to be associated with high risk of pituitary dysfunctions (Severe > Moderate > Mild)<sup>5,7,16,19,22,24–28</sup> and it has been suggested that patients who suffer head trauma should routinely undergo endocrine evaluation.<sup>25</sup> Contrary to these findings few studies found no associations of hypopituitarism with severity of TBI,<sup>7,22,26–28</sup> Chronic hypopituitarism that will need hormone replacement can occur in approximately 20% of patients after mild, moderate, or severe traumatic brain injury. As it is well known these major deficiencies are potentially treatable, routine pituitary hormonal testing within 6 months of injury is indicated recommended in this sub-group of patients.<sup>29</sup>

### 4. Pathophysiology

In retrospect a large number of neuropathological studies established a frequency of 26.4%–86% hypothalamic-pituitary lesions in patients with TBI.<sup>17,30–34</sup> Several mechanisms have been suggested for this hypothalamic-pituitary dysfunction due to TBI including hypoxic insult or direct mechanical injury to the hypothalamus, pituitary stalk, and/or pituitary gland; compression from hemorrhage, edema, or raised intracranial pressure; and vascular injury to the hypothalamus or the pituitary gland.<sup>6,35</sup> The hypophyseal vessels are anatomically vulnerable to shearing injuries, increased intracranial pressure and anterior base of skull fractures, and pituitary ischemia or hemorrhage described as common findings at autopsy.<sup>36</sup> Direct mechanical insult to the pituitary gland, the stalk or the hypothalamus has been proposed as stalk resection could be radiologically demonstrated in 3.9% cases in one study.<sup>37</sup> It was observed that in patients with large or medium sized pituitary infarctions had increased intracranial pressure at some point.<sup>32</sup> Interruption of the hypothalamohypophysial portal blood supply (i.e., due to increased intracranial pressure) was assumed to be the possible mechanism for anterior lobe infarction.<sup>30,32</sup> Acute infarction as the underlying adenohypophysial pathology could be confirmed in patients with TBI who did not die instantly after the trauma.<sup>34</sup> Many

autopsy studies have reported the lesions in victims of fatal traumatic brain injuries and it has been shown that there was convincing histopathological evidence of lesions involving hypothalamus and pituitary gland. In 42.5% of autopsies the lesions were in the anterior hypothalamus (typically lesions of infarction and ischemia) and in 28% of the cases pituitary lesions were also seen.<sup>31</sup> In other study patients who died due to TBI, there was an up to 50% incidence of hemorrhage in the pituitary capsule and up to 30% incidence of either necrosis of the anterior pituitary or stalk hemorrhage.<sup>37</sup> We need to remember that these autopsy studies included the most severe and fatal cases and may not reflect the pathophysiology of long-term pituitary failure in survivors.<sup>38</sup>

### 5. Clinical course

The timing of manifestation of hormonal deficiencies following TBI varies from day to years<sup>13,22,39</sup> and these have been observed between 0 and 6 months depending on the severity of the primary insult.<sup>40</sup> In one study GH deficiency was the most common pituitary deficit 1 and 3 years after TBI.<sup>39</sup> Early neuroendocrine abnormalities were transient in some patients, whereas hypopituitarism less commonly evolved over time in others. Many prospective studies analyzed the results of pituitary function at different points after TBI. In two studies, the initial assessment was performed in the acute phase first,<sup>41</sup> whereas in the other two studies, the initial assessment was performed at 3 months after trauma.<sup>5,22</sup> All studies repeated testing 12 months after trauma. In one study, endocrine testing additionally was performed 6 months after TBI.<sup>41</sup> In all studies, a trend toward improvement in pituitary function over time was observed and some of the early abnormalities were transient with complete recovery.<sup>12</sup> In other studies, new deficiencies occurred only less commonly (5%) after 3 months and these were only single axis deficiencies. Only one study evaluated pituitary function 3 and 12 months after SAH. The rate of pituitary dysfunction decreased from 47% to 38% by 1 year.<sup>42</sup> No new deficiencies occurred in patients with normal pituitary function at 3 months after SAH.<sup>42</sup>

### 6. Neuropsychiatric morbidity

Post-traumatic hypopituitarism may make an important contribution to the high rates of physical and neuropsychiatric morbidity in patients with head injury<sup>43</sup> and can affect all grades of severity of injury and can be difficult to diagnose.<sup>36</sup> Hormonal deficiency can present with a wide range of clinical manifestations, including fatigue, myopathy, cognitive difficulties, depression, behavioral changes, sodium dysregulation and adrenal crisis.<sup>36,44</sup> Excessive sleepiness, inattention, difficulty concentrating, impaired memory, an inability to learn new things, faulty judgment, irritability, emotional outbursts, disturbed sleep, diminished libido and depression can be the potential manifestations of treatable, unrecognized pituitary hormone deficiency.<sup>45,46</sup> It has been recognized that post-traumatic hypopituitarism can be independently

associated with poor quality of life, abnormal body composition, and adverse metabolic profile.<sup>47</sup>

## 7. Diagnosis

As mentioned earlier, there is a wide variation of the frequencies of hormone deficits reported. In general, assessment of the growth hormone and adrenocorticotrophic hormone axis require dynamic stimulation tests to distinctly separate normal from deficient responses and appropriate cut-offs should be defined considering potential confounding influences of assays used, laboratory tests, age, body mass index, and sex (reviewed in the study by Schneider et al<sup>11</sup>). Therefore, differences in the reported frequencies may be due to more stringent diagnostic criteria applied by some researchers but not others. The insulin tolerance test evaluates the integrity of both hypothalamic and pituitary function as opposed to many other tests and has been considered the criterion standard for the evaluation of assessing the growth hormone and the adrenal axis. However, it cannot be performed in patients with severe cardiovascular disease and uncontrolled epileptic seizures, limiting its use in patients with TBI and SAH. The insulin tolerance test has been used by some authors<sup>6,18,26,48</sup> with no adverse effects, but other authors have used alternative tests.<sup>5,7,15,16,22,41,49</sup> Different cutoff levels used for these tests and different hormone assays might have had an important influence on the frequency of patients defined as hormone deficient.<sup>50</sup> In addition, some authors used 2 dynamic tests to confirm abnormalities in pituitary function,<sup>27</sup> while in other cases only one test was used.<sup>14</sup> Therefore, the robustness of the methods used to diagnose hypopituitarism varies between studies. Moreover, the fact that hypopituitarism has been found more often in brain-injured patients than in control individuals and the fact that patients with post-traumatic hypopituitarism show the same impairments as patients with other forms of hypopituitarism underline the importance of the problem.

## 8. Imaging correlation

Many studies describe the imaging findings and their correlation with the development of post-traumatic hypopituitarism. Intracranial bleeding or diffuse cerebral edema that suggest severe TBI increased intracerebral pressure predicts post-traumatic hypopituitarism.<sup>24</sup> Abnormalities in pituitary imaging (magnetic resonance imaging or CT scans) were found in 80% of patients with TBI with hypopituitarism compared with 29% of patients without hypopituitarism.<sup>51</sup> Post-traumatic diabetes insipidus has been shown to be associated more severe head trauma and the presence of cerebral edema on CT scan.<sup>6,52</sup> However in another no association was found between hypopituitarism and CT imaging results.<sup>26</sup> Although magnetic resonance imaging (MRI) is regarded as the best imaging technique, but may fail to show pathological abnormalities in some patients with post-traumatic hypopituitarism.<sup>53</sup> The most common pathological findings are hemorrhage of the hypothalamus and posterior lobe and infarction of the anterior lobe of the pituitary.<sup>53,54</sup> In

6–7% of patients with post-traumatic hypopituitarism there may not be demonstrable abnormalities on MRI.<sup>37</sup> An association between increased pituitary volume and pituitary dysfunction following TBI has been proposed<sup>55</sup> and in 80% of patients with hypopituitarism, and in only 29% without hypopituitarism. It has reported that there is early pituitary enlargement in the acute (0–7 days) phase following severe and the pituitary volume tends to increase until three months TBI that may persist in the chronic phases,<sup>55</sup> tends to show sign of recovery by six months post-injury.<sup>54,55</sup> However this reduction in size has been questioned, whether it represent true recovery (the reductions of pituitary volumes) or whether it is a step toward further deterioration.<sup>7,54–55</sup>

## 9. Screening

The present evidence suggests that there is high risk for pituitary dysfunction following TBI and early diagnosis is mandatory not only to confirm but also to avoid life threatening albeit preventable complications.<sup>22,56,57</sup> It has been suggested that a baseline hormonal testing should be performed in patients with moderate-to-severe TBI<sup>5,36,58</sup> and in patients when there is clinical suspicion.<sup>58</sup> Patients with high risk to develop hormonal deficiency i.e. those who have extended ICU stay, raised intracranial pressure, diffuse axonal injury, or basal skull fractures should undergo assessment of pituitary functions.<sup>51,59</sup> However patients with severe disability (vegetative states) who may not benefit from hormonal replacement therapy can be excluded from non-vital hormone deficiency assessment.<sup>26,59</sup>

Early post-traumatic pituitary dysfunction can be transient in many cases and conversely, hypopituitarism can evolve over several weeks or months after injury.<sup>5,7,22,41</sup> Therefore, periodic evaluation in the first year after trauma may be necessary. With the available data, there is consensus that universal screening should be recommended in all patients with moderate-to-severe TBI (Glasgow Coma Scale – GCS – 3–12).<sup>14,59</sup> Although patients with severe disability (vegetative states) who will not benefit from hormonal replacement therapy are excluded from non-vital hormone deficiency assessment. In mild cases (GCS  $\geq$ 13), screening is indicated only if there are signs or symptoms of pituitary dysfunction. Similarly, universal screening in all patients with SAH who may potentially benefit from hormones replacement therapy is also recommended. Clinical evaluation of hypopituitarism is difficult because signs and symptoms may be subtle and unspecific and may mimic the neuropsychological sequelae of TBI.<sup>59,60</sup> Besides, clinical characteristics of mild hypogonadism, hypothyroidism or hypoadrenalism, or mild general hypopituitarism may be difficult to recognize. This is the reason why universal screening with baseline hormonal assessment seems to be the most reasonable approach.<sup>14,59</sup> Table 1 summarizes the tests to screen for hypopituitarism in traumatic brain injury. In the acute phase of brain injury, the diagnosis of adrenal insufficiency should not be missed because it can be life threatening.<sup>61,62</sup> Patients should be screened for signs and symptoms of hypocortisolism including hyponatremia, hypotension, and hypoglycemia. Because dynamic assessment of adrenocorticotrophic

**Table 1 – Screening tests for hypopituitarism following traumatic brain injury.**

Endocrine axis	Baseline tests	Provocative tests
Pituitary–adrenal axis	Morning cortisol	ACTH, ITT, CRH
Pituitary–thyroid axis	TSH, fT4, fT3	TRH
Pituitary–gonadal axis	LH, FSH, testosterone (men), estradiol (women)	
Growth hormone assessment	GH, IGF-1	ITT, glucagon, arginine, GHRH, clonidine

hormone reserve is not practical under conditions of acute critical illness, we suggest that morning serum cortisol concentrations be checked in the first days after trauma or SAH.<sup>62</sup> Defining a cortisol cut-off that will help diagnose adrenal failure in acute illness is difficult because serum total cortisol values under such conditions will be influenced by several factors including the degree of severity of the underlying illness, sepsis, and medications.

Serum levels of cortisol-binding globulin can be reduced in catabolic states resulting in disproportionately low total cortisol compared with free (biologically active) cortisol (clinical laboratory tests that only measure total cortisol as free cortisol is technically difficult, time-consuming and expensive). Allowing for these confounding factors, acute phase morning cortisol level of less than 7.2 µg/dL (200 nmol/L) may be suggestive of adrenal insufficiency in acutely ill patients with TBI or SAH, and glucocorticoid replacement should be instituted.<sup>41</sup> However, values between 7.2 and 18 µg/dL (200–500 nmol/L) in the presence of features suggestive of adrenal insufficiency such as hyponatremia, hypoglycemia, hypotension, or unexpected slow recovery may still be inappropriately low and a trial of glucocorticoid therapy should be considered.

Assessment of the growth hormone, gonadal, and thyroid axes is not necessary in the acute phase because there is currently no evidence that acute-phase therapy with these hormones improves outcome. Between 3 and 6 months after injury, all patients should undergo careful screening for clinical signs of hypopituitarism. Particular attention should be paid to loss of secondary hair, new onset of oligomenorrhea or amenorrhea, impaired sexual function, weight changes, polydipsia, the above-mentioned signs of hypocortisolism, and poor recovery. If any of these signs is present, pituitary assessment should be performed. Because the sequelae of brain injury may mask the signs of hypopituitarism, the threshold for endocrine assessment should be low and in cases of uncertainty, endocrine assessment should be performed at least once. Also, in patients with basal skull fractures, diffuse axonal injury, increased intracranial pressure, or prolonged intensive care unit stay, pituitary assessment should be considered. If hypopituitarism is detected, hormone therapy should be given as appropriate. In patients with documented anterior hypopituitarism at 3–6 months post-

injury, repeat pituitary assessment at 1 year may be considered if the clinical or biochemical parameters raise the possibility of delayed recovery.

## 10. Conclusions

Although most cases of post-traumatic neuroendocrine dysfunction seem to be transient, persistent mild deficiency of pituitary hormones can be easily missed, as patients may have less-severe symptomatology and their post-traumatic clinical course is often complicated by significant neurological and cognitive disabilities. Presently there is paucity of prospective data on the natural history of post-traumatic neuroendocrine dysfunctions and there is need to develop appropriate guidelines for follow-up of suspected to have these dysfunctions so the information can lead to timely and appropriate assessment and treatment of hormonal deficits.

## Conflicts of interest

All authors have none to declare.

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