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Traumatic brain injury induced neuroendocrine changes: acute hormonal changes of anterior pituitary function

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Abstract

Purpose It is estimated that approximately 69 million individuals worldwide will sustain a TBI each year, which accounts for substantial morbidity and mortality in both children and adults. TBI may lead to significant neuroendocrine changes, if the delicate pituitary is ruptured. In this review, we focus on the anterior pituitary hormonal changes in the acute post-TBI period and we present the evidence supporting the need for screening of anterior pituitary function in the early post-TBI time along with current suggestions regarding the endocrine assessment and management of these patients.

Methods Original systematic articles with prospective and/or retrospective design studies of acute TBI were included, as were review articles and case series.

Results Although TBI may motivate an acute increase of stress hormones, it may also generate a wide spectrum of anterior pituitary hormonal deficiencies. The frequency of post-traumatic anterior hypopituitarism (PTHP) varies according to the severity, the type of trauma, the time elapsed since injury, the study population, and the methodology used to diagnose pituitary hormone deficiency. Early neuroendocrine abnormalities may be transient, but additional late ones may also appear during the course of rehabilitation.

Conclusions Acute hypocortisolism should be diagnosed and managed promptly, as it can be life-threatening, but currently there is no evidence to support treatment of acute GH, thyroid hormones or gonadotropins deficiencies. However, a more comprehensive assessment of anterior pituitary function should be undertaken both in the early and in the post-acute phase, since ongoing hormone deficiencies may adversely affect the recovery and quality of life of these patients.

Keywords Traumatic brain injury (TBI) · Post-traumatic hypopituitarism (PTHP) · Anterior pituitary hormone deficiency · Acute post-TBI period

Introduction

Traumatic brain injury (TBI) is an acquired insult to the brain resulting from external mechanical forces, blast waves, or penetration by a projectile. TBI accounts for substantial morbidity and mortality in both children and adults. It is estimated that approximately 69 million individuals worldwide will sustain a TBI each year [1]. However, it is worth noting, that the incidence is probably underestimated as these numbers refer to TBI patients admitted to hospital. Indeed, many patients who sustain a mild TBI (sports concussions, falls, low-velocity road traffic accidents) probably never seek medical attention.

TBI may not only cause structural and functional derangement within the brain but importantly can also lead to significant neuroendocrine changes. Several alterations in hormone levels may become apparent during the first hours or days after injury. In this review, we focus on the anterior pituitary hormonal changes in the acute post-TBI period. In particular, we present the evidence supporting the need for screening of anterior pituitary function in the early post-TBI time along with current suggestions of how to proceed regarding the endocrine assessment and management of these patients. To this end, original systematic articles with prospective and/or retrospective design studies of acute TBI were included, as were review articles and case series.

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Epidemiology

The frequency of anterior pituitary dysfunction leading to post-traumatic hypopituitarism (PTHP) varies according to the severity and the type of trauma, the time elapsed since injury, the study population, the design and endocrine testing, and the criteria used to diagnose anterior pituitary hormone deficiency. A systematic review of 66 studies (5386 patients) estimated the prevalence of anterior pituitary disorders according to the time of hormonal assessment after the injury (< 3, 3–12, and > 12 months after TBI). In studies evaluating all pituitary axes, 45% of patients had hypopituitarism in the acute phase (< 3 months), 36% in the mid-term (3–12 months) and 32% had long-term hypopituitarism, as defined by at least one anterior pituitary hormone disorder. The authors reported that anterior pituitary disorders in TBI were associated with a trend of increased risk of death in the intensive care unit, but not with unfavorable neurological outcome. Moreover increased age, TBI severity, and skull fractures were associated with a greater risk of developing anterior pituitary disorders, whereas sex and brain edema at admission CT scan were not [2].

Pathophysiology

The pathophysiology of post-traumatic pituitary damage is complex. It involves primary focal insults as well as secondary damage due to edema, hemorrhage, hypotension, and hypoxia [3, 4]. The pituitary gland, due to its anatomical location within the restricted sella turcica area, is particularly vulnerable to edema. Fragility of the infundibular hypothalamic structure and vascular supply represent additional risk factors. In fact, the hypophyseal portal vessels passing through the diaphragm sella to supply the anterior pituitary are particularly susceptible to mechanical injury and compression [3, 4].

The role of hemorrhage is largely substantiated from postmortem findings revealing capsular, pituitary and hypothalamic hemorrhage and infarcts [5–10]. Hemorrhage in the anterior lobe has been identified particularly in those patients with short survival periods, whereas infarcts have developed in patients surviving at least 14 h [8, 10].

In addition, MRI studies have also contributed to delineate pituitary changes in the acute post-TBI period. Significant pituitary gland enlargement due to edema was demonstrated in an MRI study of 41 moderate/severe TBI patients during the acute phase. Thirty percent (30%) of the patients in that study showed focal changes in the pituitary gland (hemorrhage/hemorrhagic infarction, swollen gland with bulging superior margin, heterogeneous signal intensities in the anterior lobe and partial transaction of the infundibular stalk) [11]. MRI diffusion-weighted imaging has enabled early and noninvasive detection of microstructural brain damage. The apparent diffusion coefficient (ADC) provides an initial measure of movement of water molecules limited by interactions of the diffusing molecules within cellular structures. In human studies of the early TBI period, decreased pituitary ADC values have been observed and such changes are considered to reflect microstructural pathology [12].

The incidence of PTHP in mild TBI is low [13–19] but increases in studies of patients with moderate/severe injury [20–25]. In fact, there is a significant correlation between the severity of head injury (most commonly measured with Glasgow Coma Scale score) and acute PTHP (13). Lack of significant associations with TBI severity reported in some studies may be attributed either to the small number of patients included in each subgroup (mild, moderate, severe TBI) or to the lack of subclassification. It should be noted that pituitary axes may be differentially affected and data for each axis are presented in relevant sections of this review.

Acute hormonal changes of anterior pituitary

Hypothalamo-pituitary adrenal (HPA) axis

It is well recognized that immediately after head injury several changes of the HPA axis occur in the context of the acute injury response, including an increase in serum cortisol, abolition of diurnal rhythm and inadequate suppression after dexamethasone [16, 18, 21, 26–37]. These changes are mediated by ACTH or ACTH-independent drivers (sympathetic nervous system, immune system, cytokines). Moreover, during the acute phase of critical illness several changes also affect cortisol availability through the reduction of cortisol breakdown and the decrease of cortisol binding globulin concentration [38]. The rise of cortisol represents an adaptive mechanism and, increased cortisol levels gradually decline [21, 33, 37, 39, 40]. In a prospective study evaluating 100 moderate/severe TBI patients, 38% had high cortisol levels on day-1 and 21% on day-7 respectively [37]. Similarly, Hohl et al reported high cortisol levels in the first 10 h post severe TBI in 49% of male patients and in 23.5% during the next 30 h [40]. In agreement, Tandon et al reported that cortisol rose within 24 h after severe TBI in 52.5% of patients, remained elevated for a prolonged period and, gradually declined over a 6-month period to become low in 4% of patients at the end of 6-month follow-up [34].

Table 1 Studies that evaluated HPA axis in the acute post TBI period

	N	TBI severity	Time from TBI	Test	Acute HPA axis changes	Follow up/recovery
Feibel [29]	23 (18 males)	Severe	12–36 h	Basal F,ACTH	Decreased F < 5 μg/dl in patients with normal ICP and normal brain stem function or dysfunction, or increased ICP and brain stem dysfunction, increased F in patients with elevated ICP and normal brain stem function independently of ACTH	
Barton [30]	For cortisol (17 males, 7 females) for ACTH (9 males, 6 females)	Severe	Day 0 (2–12 h)	Basal F,ACTH	Non significant tendency of F to decrease at higher severity scores	
Hackl [39]	21 (16 males)	Severe	Acute	Basal levels cortisol, 11-deoxycortisol, DHEAS	Mean cortisol level 121.3 nmol/l, low levels DHEAS, 11-desoxycortisol was elevated in the group with GCS < 6	
Della Corte [32]	22 (males)	Severe	Days 2,3,4,5,6,7,15	Basal F	A trend toward a progressive decrease was observed for cortisol concentrations from days 2 to 7 and on day 15	
Cernak [33]	31 males	Mild/severe/blast injury	Days 0,1,2,3,5,7	Basal F	Increase of cortisol which persisted for 1 day and normalized the 2nd day in group GCS (13–15) and indirect head trauma but dropped sharply in the GCS (4–6) group and persisted for 1–3 days	
Agha et al. [54]	50 (38 males)	Moderate/severe	First (7–20) days, (median 12 days), 6 and 12 months	Basal levels F, ACTH/ Glucagen stimulation test (GST)	16% (as by GST) ACTH deficiency	50% recovered after 12 months
Dimopoulou [15]	51	Mild/moderate/severe	Days (1–60)	Basal F/ACTH, low dose corticotropin stimulation test	15.6% (as by low dose corticotropin test) had adrenal hyporesponsiveness	

Table 1 (continued)

	N	TBI severity	Time from TBI	Test	Acute HPA axis changes	Follow up/recovery
Dimopoulou [15]	40 (33 males)	Moderate/severe	Days (7–60)	Basal F/ACTH, low dose corticotropin stimulation tast, CRH test	15% (as by low dose corticotropin test) and 16% (as by CRH test) had adrenal hyporesponsiveness	
Cohan [20]	80 (65 males)	Moderate/severe	Days (0–9)	Basal F/ACTH twice daily for 9 days	53% ACTH deficiency	
Tanriverdi [44]	52 (43 males)	Mild/moderate/severe	Day 0, 12 months	Basal F/ACTH	9.8% ACTH deficiency	(4/5) 80% recovery in 12 months
Klose [16]	46 (33 males)	Mild/moderate/severe	Days (0–12), (3,6,12 months)	Basal F/ACTH, synacthen test	4% ACTH deficiency	At 12 months 100% recovery
Kleindienst et al. [35]	71 (57 males)	Mild/moderate/severe	Days (0,3,7) 24–36 months	Basal F/ACTH	Low F (< 10.5 µg/dl) (22%) on day 0, (25%) on day 3, and (18%) on day 7	At (24–36) months: recovery 39% (as by basal F), 57% as by synacthen test
Tandon et al. [34]	99 (87% males)	Severe	Days (0,15, 90, 180)	Basal F	(31/59) high F on day 0 (28/50) normal F on day 0, (23/54) high F on day 15, (31/54) normal F on day 15	(15/51) high F on day 90, (33/51) normal F on day 0, (11/48) high F on day 180 and (35/48) normal F on day 180
Krahulik et al. [17]	186	Mild/moderate/severe	Acute phase, 3,6,12 months post injury	Basal F/ACTH	10% ACTH deficiency	3 months:(55%) recovery, in the next 3 months (8%) recovery, in the last 6 months 2 pts recovered
Wagner et al. [21]	117 (89 males)	Severe TBI	Days (0–7)	Basal F	41.9% ACTH deficiency	
Olivekrona 2013	45 (30 males)	Severe	Day 1 Day 4	Basal F	(52.3–54.5)% (< 276 nmol/l) (15.9–18.6)% < 100 nmol/l (59.1–70.5)% (< 276 nmol/l) (22.7–24.4)% (< 100 nmol/l)	
Hannon et al. [22]	100 (84 males)	Moderate/severe	Days (1–10)	Basal F (on days 1,3,5,7)	78% (< 300 nmol/l)	61.5% on day 10
Kakati et al. [36]	30 (23 males)	Moderate/severe	24 h post TBI	Basal F	Low cortisol (3.3%), high (80%)	
Hohl et al. [40]	60 males	Severe	10 and 30 h post TBI	Basal F	First 10 h (high F 49%, low F 11.8%), first 30 h (high F 23.5%, low F 21.6%)	
Prasannaet al [37]	100 (88 males)	Moderate/severe	First 24 h and day 7	Basal F	Day 1 (high F 38%, low F 2%), day 7 (high F 21.27%, low F 2.12%)	

Table 1 (continued)

	N	TBI severity	Time from TBI	Test	Acute HPA axis changes	Follow up/recovery
Alavi et al. [41]	58(41 males)	Mild/moderate/severe	Days (0–7), 6 and 12 months	Basal F/short synacthen	(6/58) 10.% low F (< 200 nmol/l, 5 normal synacthen, 1 partial ACTH deficiency	2 patients recovered after 6 months
Dalwadi et al. [18]	49 (41 males)	Mild/moderate/severe	First 24 h	Basal F/ACTH	12.24% F < 7 µg/dl	
Kumar et al. [19]	56 (44 males)	Mild/moderate/severe	Days (0–10), 6 and 12 months	Basal F, ACTH, ITT, synacthen	(7/56) (12.5%) hypocorti-solism	(18.75%) recovery, 1/32 patient had persistent hypocortisolism
Tolli et al. [25]	56 (41 males)	Moderate/severe	Day 10 (3, 6, 12 months)	Day 10:synacthen test, basal F at (3,6,12 months)	(22/54) (41%) low F, 11% subnormal increase at synacthen	
Bensalah et al. [23]	277 (257 males)	Moderate/severe	Days (0–7), 3 months	Basal F, ITT in the recovery phase (3 months later)	2.9% ≤83 nmol/l, 20.2% ≤276 nmol/l, 35.4% ≤414 nmol/l	At 3 months AI in all 3 pts < 83, in (12/24) < 276, (4/16) < 414

Several studies have now shown diminished cortisol responses in varying proportions of patients during the acute post-TBI period (Table 1). Recognition of glucocorticoid deficiency in the acute phase of TBI is vital, because it is associated with a poor neurological outcome, a greater need for vasoactive drug therapy, hyponatremia, relative or absolute hypoglycemia, hemodynamic instability, and rapidly progressive hypotension, all of which may increase the risk of morbidity and mortality [15, 20, 22, 23]. Studies that evaluated adrenal dysfunction in the acute post-TBI time report a wide variation in the incidence (from 2 to 78%) of adrenal failure, due mostly to differences in study protocols (different diagnostic cut-offs, evaluation of basal or stimulated cortisol, number of time point cortisol measurements, number of patients and their subclassification proportion according to the severity of TBI, male/female ratio, age spectrum) [15, 17–24, 35–43]. In a large-scale study Bensalah et al, evaluated ACTH deficiency in 277 patients with severe/moderate TBI using 3 different cortisol cut-offs. In this study, 2.9% had very low levels (≤83 nmol/l), 20.2% had cortisol levels ≤276 nmol/l (a value indicating adrenal deficiency in critical illness according to the consensus statement by the American College of Critical Care Medicine) and 35.4% had levels of ≤414 nmol/l [23].

A limited number of studies have evaluated HPA axis in the acute post-TBI interval not only with baseline measurements but also with stimulation tests. Dimopoulou et al studied 40 patients with moderate/severe brain injury (7–60) days after trauma and demonstrated that 15% of them failed the low-dose ACTH test. Interestingly these patients required more frequently and for a longer time interval vasopressors during ICU hospitalization and, exhibited higher IL-6 levels compared to TBI patients with a normal response to the low-dose ACTH test [42]. On the same line Agha et al, [43] diagnosed ACTH deficiency in 16% of 50 moderate/severe TBI patients during the first (7–20 days) post-TBI. ACTH deficiency was defined by failure to increase cortisol > 450 nmol/l at the glucagen test. Basal cortisol concentrations were significantly lower in the group with the sub-adequate cortisol responses to glucagen compared to the responders and to healthy controls. On contrary, in a group of 46 patients (22 mild /9 moderate/15 severe TBI) Klose et al reported that only 2/46 (4%) had an insufficient 30 min cortisol response to ACTH-stimulation (449 and 379 nmol/l, respectively) and interestingly both patients had mild TBI [16].

It is important to notify that as serum cortisol levels are highly dynamic in the days after TBI, studies with only a single time point measurement or after dynamic stimulation may underestimate the true incidence of pituitary dysfunction. To this end, it is worth noting that prospective studies with serial cortisol assessments report higher incidence of adrenal insufficiency. Thus, Kleindienst et al who studied

a group of 71 patients (24 mild/11 moderate/24 severe TBI) demonstrated that the incidence of low cortisol levels (< 10.5 μg/dl) was 22% on day-0, 25% on day-3, and 18% on day-7. Interestingly, on day-7 the urinary excretion of free cortisol and cortisone was elevated (> 60 μg/24 h and > 140 μg/24 h) in 11/13 patients, and the respective sum of metabolites, was above the normal range in 7/13 patients suggesting that the normal circadian variation of cortisol is replaced by a more continuous secretion under severe stress [35]. Even higher figures of adrenal insufficiency (AI) were documented by Cohan et al. Remarkably in that study paired cortisol and ACTH were measured twice daily during the first 9 days post injury both in the TBI and in the control group. The authors reported that fifty percent (50%) of 80 patients (23 moderate/57 severe TBI) had AI defined as two consecutive cortisols of < 15 μg/dl or one cortisol of < 5 μg/dl [20]. Similarly, Olivecrona et al demonstrated that 54% of 45 severe TBI patients on day-1 and notably 70% on day-4 had morning cortisol (< 276 nmol/l) [24]. In a meticulous study of 100 patients with severe/moderate TBI Hannon et al, measured sequentially morning 9:00 am cortisol levels on days 1, 3, 5, 7, 10 and documented that 78% had at least 1 measurement of < 300 nmol/l. Most patients developed low plasma cortisol levels on days 1–3 when serum cortisols in the comparison group were at their highest; recovery occurred by day 10 in 61.5% [22].

Cortisol changes during the first 7 days after severe TBI have also been evaluated by group trajectory analysis (TRAJ) which resulted in 3 distinct TRAJ groups: a high, a decliner, and a low group with different incidence of adrenal failure. The high group had the highest cortisol levels throughout the sampling period and only 3% of adrenal failure. Levels for the low group started high and declined over time to reach control levels by day 3 while they began to rise again by day 4. In that group AI was 62%. The decliner group levels started high, continued to decline over the entire sampling period and had the higher level of AI (65%). That study pointed out that older age was associated with the high TRAJ cortisol group [21].

Discrepancies between the severity of the injury and cortisol levels have been reported, with either a positive [16, 18, 35, 37], negative [13, 16, 30, 37] or lack of correlation [34, 44]. A few studies have demonstrated a positive correlation between Glasgow Coma Score (GCS) and cortisol levels in patients with mild or moderate TBI, but interestingly this was not demonstrated in a study with 100 moderate/severe injured patients which showed high levels of hypocortisolemia [22]. Bensalah et al found a relationship between the presence of intra-parenchymal hematoma and acute AI but this was not confirmed by other studies [24, 43]. Finally, it should be noted that the use of medications such as pentobarbital, propofol, etomidate is strongly associated with lower cortisol levels [20, 23]. Propofol and etomidate blunt steroidogenesis while pentobarbital induces hepatic microsomal enzymes and increases corticosteroid metabolism.

To summarize, most existing data from well-designed prospective studies indicate a relatively high prevalence of AI in the early-post TBI period [20–23, 25, 35, 44]. Hypocortisolemia seems to be associated with younger age, greater injury severity, early ischemic insults and has a significant impact on patients outcome in the acute setting [20, 23].

Somatotrophic-IGF1 axis

In the majority of studies on GH-IGF-1 status in the acute phase of TBI only basal GH and IGF-1 levels were examined. The data regarding basal GH levels in the acute phase of TBI are inconsistent [39]; low [45, 46], high [18, 31, 39, 46, 47], or normal levels [32] are reported. It is worth mentioning that given the known pulsatility of GH secretion the true status of GH release in the acute setting may not be well delineated by once-daily measurements. IGF-1 and IGFBP-3 levels are usually falling in the first 48–60 h [45], but in many cases [18, 24, 32, 35, 40] they recover during the next post-traumatic days [24] or weeks [32, 46]. It is speculated, that this IGF-1 drop is due either to a state of acquired peripheral GH resistance or to transient somatotroph suppression [44]. No correlation of IGF-1 levels with the severity of injury has been reported [16, 18, 44] but Wagner et al demonstrated that a younger age and anemia were associated with suppressed IGF-1 levels, while older age and higher BMI were associated with acutely low GH [46].

Dynamic GH assessment in the early post-TBI period has been performed in a limited number of studies. However, there is no agreement on which particular test evaluates best these patients. Agha et al, estimated that after glucagen stimulation 18% of patients had a peak GH level < 5 ng/ml and 6% a peak < 3 ng/ml. IGF-1 levels were not different between GH-deficient and GH-sufficient patients and GH deficiency was not related to patients' age, BMI, or initial GCS [43]. On the same line, Dimopoulou et al reported that 9% of patients had a partially impaired GH response after GHRH administration [48]. To summarize, during the first days after complicated mild, moderate, or severe TBI, circulating levels of IGF-1 decline in the majority of patients [45], while GH fluctuate from low, normal to mildly elevated levels [18, 31, 32, 39, 45–47].

Thyroid axis

Acute TBI induces various alterations in thyroid hormone levels, typical of the low T3 syndrome. The levels of T4, FT4, T3 correlate significantly with the severity of head injury [31, 49–51]. Several groups report rapid decreases

in T4 and T3 levels [18, 32, 33, 39, 40, 50–52] while others noticed no significant changes in serum T4 [32, 33, 43]. In severe TBI, low [16, 31, 33, 35, 40, 43, 52] or normal [32, 34, 37, 50] TSH levels have been demonstrated. On contrary, in mild TBI, the levels of TSH and T3 may increase [33]. Low FT4 without elevated TSH levels, suggesting TSH deficiency, is described in 5–15% of patients with moderate/severe TBI [16, 35, 37, 43, 44, 48] and usually is transient [35]. As the patients recover, thyroid hormones return to normal, even from the first days in mild cases [33] or over weeks [13, 31, 33, 37, 43, 44]. Indeed restoration of the pituitary thyroid axis is associated with a less severe injury and a more favorable outcome at 3 months [24].

Prolactin

The data regarding prolactin levels following TBI are conflicting. Several studies report elevated [4, 18, 43, 53, 54], normal [31, 51, 52] or low levels [39]. Post-traumatic hyperprolactinemia can be mediated by physical stress, damage to the hypothalamus or the pituitary stalk or caused by antidopaminergic medications [4]. The severity of TBI is negatively correlated with prolactin levels [18, 31, 44, 54] and a lower PRL response after TRH administration has been reported in severely injured patients [53]. Of note, in comatose patients a paradoxical response of PRL to GHRH has been associated with a good outcome [32].

Gonadal axis

Suppression of the hypothalamic–pituitary–gonadal axis has been reported in 13–80% of patients following head injury [16–19, 24, 33, 35, 36, 39, 40, 43, 44, 46, 52, 55–57]. This represents an adaptive process, as the metabolism is directed away from the expense of the reproductive system so as to manage the acute injury response [58]. Excessive stress hormones can inhibit the hypothalamic-pituitary-gonadal (HPG) axis function, suggesting a possible role for TBI-induced hypercortisolemia as a cause of injury-induced hypogonadotropic hypogonadism [59]. In fact in the study by Ranganathan et al, menstruation resumption among premenopausal women occurred when serum cortisol normalized to luteal phase control levels. For post-menopausal women, serum cortisol reductions corresponded with resolution of suppressed LH levels [59]. Both testosterone in men and estrogen in women significantly fall within the first 24 h [16, 17, 24, 33, 35, 39, 40, 43, 44, 46, 52, 55, 57, 59]. Testosterone levels correlate with the severity of head injury in a few studies [16, 33, 39, 43, 44, 52], but not in others [18, 19, 24, 39, 57]. Gonadotropins decrease [16–19, 24, 35, 36, 39, 43, 44, 46, 52, 55, 60, 61], independently to hyperprolactinemia [43] and they respond to (GnRH) administration [51, 52, 55, 61]. Therefore, suppression of the gonadal axis is very common in the early time after TBI. The degree of this suppression relates to the severity of injury and has prognostic implications [16–19, 24, 33, 35, 36, 39, 40, 43, 44, 46, 52, 55–57, 59–61].

Acute hormonal changes of anterior pituitary in children

Only few studies have evaluated anterior pituitary function in the early post-traumatic period in children and adolescents (Table 2). Srinivas et al studied 37 children on the 1st, 3rd, and 7th day after severe TBI, and found that ACTH and cortisol were elevated on the day of injury and normalized on days 3 and 7. ACTH was significantly elevated in 63% of patients with frontotemporal injury but only in 13% of those without. A similar but not significant trend was seen with cortisol levels; 63% of patients with a fronto-temporal injury had elevated cortisol (versus 40% without). Elevated cortisol was less common among those with a more severe injury (GCS 3–4). 46% and 14% of children had a low cortisol and ACTH respectively. Thyroid hormone levels were related with prognosis; 94.4% of children with good prognosis and 58% of children with poor prognosis had normal T3 levels on the 1st day of trauma. Normal fT4 was two times more common among patients with "good" outcome compared to those with "poor" outcome [62]. In contrast, in another retrospective study none of the children had low cortisol levels in the early post-TBI period [63].

Ulutabanca et al reported that amongst 41 children 44% had at least one pituitary hormone dysfunction during the acute post-TBI period; (17% TSH, 2% FSH/LH, and 24% ACTH deficiency). Cortisol levels were high in severe trauma, and low in moderate trauma. Euthyroid sick syndrome occurred in 49% and central hypothyroidism in 17% of children. High PRL levels were detected in 7%. In one of the 2 patients in mini-puberty period, the gonadotropic hormone levels were low, but no long-term data are provided for their follow up. In pubertal children no hormone dysfunction was observed. When acute and chronic hormone values were compared, TSH, fT3, fT4, LH, IGF-1, and ACTH levels were significantly lower in the acute period. The changes in the acute period were totally recovered in the chronic period suggesting an adaptive response [64].

Another study of 58 children and adolescents demonstrated that 45% suffered from central hypothyroidism and 25% of adolescents had hypogonadotropic hypogonadism. Hyperprolactinemia was detected in 35% and an increase in cortisol and ACTH levels in 10%. IGF-1 levels were low in 5 cases. In nearly all patients, these changes were transient (except for two with unresponsive wakefulness syndrome). The incidence of endocrine dysfunction at the acute phase significantly

Table 2 Studies that evaluated acute hormonal changes of anterior pituitary function in children and adolescents

	N	TBI severity	Time from TBI	Test	Endocrine abnormalities
Srinivas et al. [62]	37 (27 males)	Severe	Days (1,3,7)	Basal F, ACTH, TSH, T3,T4, FT4, GH, PRL	Elevation of cortisol and ACTH on day 1 followed by reduction on day 3 and 7 On day 3, 57% and 39% of T3 and T4 levels were subnormal Mild hyperprolactinemia on days 3 and 7
Einaudi et al. [63]	Prospective group 30 patients (23 males)	Severe/moderate/mild	Within 72 h (T0), 6 months (T6), 12 months(T12) for the prospective group	Basal ACTH, F, FT3, FT4, TSH, PRL, IGF1, FSH, LH, E2/TESTO in pubertal and postpubertal children, GHRH + arginine, LHRH, glucagen in T6, T12	(T0): no ACTH deficiency, low T3 syndrome in 7/30, (T6): one with ACTH deficiency, (T12): one with GH deficiency
Ulutabanca et al. [64]	41 (27 boys)	Sever/moderate/mild	First 24 h and 12 months after injury	Basal TSH, FT3,FT4, PRL, ACTH, F, FSH, LH, E2/TESTO, GH/IGF1 in the acute phase, GHRH + arginine test in chronic phase	In acute period, 44.3% had at least one pituitary hormone dysfunction (17.1% TSH,2.4% FSH/LH, and 24.4% ACTH deficiencies), (7.3%) had high PRL, pubertal children had normal hormones,1 patient in minipuberty had low gonadotrophins 12 months: 100% recovery
Krahulik et al. [65]	58 (37 boys)	Moderate/severe	Days (2–14), 3, 6, 12 months	TSH, FT4, FT3, F, ACTH, IGF1, PRL, FSH, LH, E2/TESTO	(T0) 45% central hypothyroidism; 25% of adolescents had hypogonadotropic hypogonadism, 35% high PRL, and 10% high F and ACTH, low IGF-1 in 5 patients T3: 2 boys with combined pit deficiencies T6: 1 boy with precocious puberty and 1 with GH deficiency T12: 5 new deficiencies

correlated with the severity of injury, but it was not an indicator for the development of a late hormonal disorder [65].

Impact of acute endocrine changes on outcome

Early post-traumatic hypocortisolism is the most distressing outcome, as it may lead to hypotension, hyponatremia, hypokalemia, metabolic acidosis, hypoglycemia and eventually death [22, 54]. Mortality is higher in patients with low cortisol levels in the acute period [22, 23]. Higher serum GH has been measured in patients who survived for 3 months in comparison with no survivors [24, 35]. In 2 studies the levels of IGF-1 were not predictors of mortality [24, 40]. GH and IGF-1 receptors are widely present in the brain. GH is directly involved in vascular reactivity and CNS repair after hypoxic injury and, IGF-1 appears to be an important factor in myelination, and protection of oligodendrocytes from tumor necrosis factor-α induced apoptosis [66]. Therefore, acute GH deficiency may have deleterious impact on the early post-TBI neuroprotective and repair processes. A reduced GH pulsatile release and a blunted response to arginine stimulation (24–48 h) after severe TBI have been associated with poor outcome [39]. Gottardis et al, [67] reported a significant GH rise after GHRH stimulation in survivors after severe TBI, whereas GH response was blunted in those who died. By contrast, Della Corte et al reported a progressive increase of GH response to GHRH from day 2 to 7 after trauma and a paradoxical response of GH to TRH in patients with unfavorable outcome [32]. King et al demonstrated that i.v. glucose administration resulted in a paradoxical increase in GH levels, which was greater in patients with worse neurological function [68]. Low thyroid hormone levels [18, 24, 33, 44, 49] and a flat TSH response to TRH stimulation [39, 50] have been associated with poor prognosis. Association between testosterone levels and mortality or morbidity was significant in one study [24], but not significant in four others [18, 21, 40]. Low LH levels in males have been correlated with lower mortality [21, 24, 40], but its prognostic role in females remains unknown. Wagner et al delineated TBI subpopulations with unique hormone profiles as risk factors for poor outcome and found that increased estradiol and testosterone levels over time were associated with increased mortality and worse global outcome for both men and women [21].

Natural history of post-traumatic hypopituitarism

The early post-TBI neuroendocrine dysfunction may be transient, but additional late abnormalities may appear during the course of rehabilitation. There are only a few studies that have evaluated prospectively (for 12–24 months) patients with acute post-TBI anterior hypopituitarism and the data are rather controversial. Krahulik et al reported that amongst patients presenting with at least one hormonal deficiency, 55% had recovery of their pituitary function by 3 months, and 74–85% within a year [17]. In their prospective study Tanriverdi et al, observed that after 1 year, recovery happened in 58%, and new hormone deficiencies appeared in 52% of patients [44].

In another prospective study in which central hypogonadism or hypothyroidism were present in 76% of patients, 13% of them failed the subsequent 3 month post-TBI testing, while at 12 months 1 patient recovered, and none developed new insufficiencies [16]. The most prevalent anterior pituitary deficiency was GH (11%) followed by ACTH (6.5%), TSH (2%), LH/FSH (2%) [16]. Hormonal evaluation of severe brain injured patients in a median time of 3.3 months post-traumatically has showed that the most prevalent hormonal alterations were increased concentrations of stress-related hormones (cortisol, prolactin, IGF-1), followed by decreased gonadal and thyroid hormones [69].

Persisting low cortisol levels have been observed in 32% of the cases at 3 months [25], in 16.6–50% at 6 months [25, 41, 54], and in 35% at 12 months post-TBI [25]. In the prospective study by Bensalah et al [23], the prevalence of persistent AI at 3 months was related to the cut-off level used to define AI, and was 100% at level < 83, 50% at level 83–276, 25% at level 277–414 and 30% if a level of > 414 nmol/l was considered. In two other studies acute basal cortisol did not correlate with dynamic cortisol response neither at 3 months nor after 2 years [23, 35]. Moreover in two prospective studies [35, 44] the prevalence of ACTH deficiency increased in the long term, from 10% in the acute phase, to 19% at 12 months in one study [44], and from 22% on admission, to 61% after 24–36 months in another [35].

Other groups have demonstrated that hypocortisolemia in the acute phase is strongly associated with the development of chronic hypopituitarism of any pituitary axis [22, 41]. Hannon et al, [22] found that all patients with chronic pituitary deficit had suffered from either acute hypocortisolemia or acute central diabetes insipidus (CDI) during their admission with TBI. Overall, at 6 months 34% had 1 pituitary hormone deficit and 3% had 2 deficits (ACTH and GH), which was far less than those having acute hypocortisolemia. Alavi et al, [41] reported that amongst 6 patients with acute hypocortisolemia 5 recovered their adrenal function but 2/5 (40%) developed abnormalities in other pituitary axes, with one patient having low LH and testosterone levels and another having low TSH and fT4 levels. In addition 10 patients with normal cortisol in the acute phase were found to have developed some form of hypopituitarism after 6 months.

In the study by Agha et al, [54] 8 patients (16%) showed subnormal acute cortisol response; at 6 months 4/8 (50%)

patients had recovered and 5 new deficiencies were detected; resulting in 9 patients with persistent abnormalities at 2 months.

In the same study [54] 9 patients (18%) had early GH deficiency, at 6 months, 5/9 (56%) had recovered and 2 new deficient patients were detected; while at 12 months, 1 patient had recovered, leaving 5 patients (10%) with GH deficiency. On contrary, Tanriverdi et al [44] reported an increase in the prevalence of GH deficiency from 20.4% in the acute phase to 38% 12 months after TBI. Acute IGF-1 levels predicted long-term GH status; and specifically a cut-off of 84 ng/ml for IGF-1 had an estimated value of 33% for GH deficiency after 1 year. Similarly Kleindienst et al demonstrated deterioration of somatotroph function as 41% had low IGF-1 immediately post-TBI, while 2 years later 57% had low IGF-1 and 35% responded < 9 ng/ml after GHRH-arginine stimulation [35].

Recovery of acute gonadotropin deficiency was observed in 3 studies [35, 44, 54]. In the first 13% had an early gonadotropin insufficiency, but none at follow-up [35]. In the second study, 41.6% were hypogonadal on admission, but only 7.7% after 12 months [44], while in the third study 80% of the patients were initially deficient, 73% recovered by 6 months and 85% by 12 months [54]. It is assumed that testosterone levels may restore after 3–6 months [35] or remain low [25, 55]. One study suggested that the early (week 1) levels of testosterone and estradiol may be helpful in predicting hypogonadism [70].

Data regarding thyroid function are more conflicted as in the study by Agha et al [54] acute TSH deficiency was present in 1 patient and it recovered by 6 months, while 1 new case was diagnosed at 6 months, and persisted at 12 months. Tanriverdi et al [44] reported that 6% of the patients had TSH deficiency both on admission and at 12 months after TBI. Transient thyroid dysfunction was described by 2 other groups. In the first biochemical acute hypothyroidism was seen in 13/55 (24%) of patients [25] but 0/52 (0%) had low levels of fT4 at 12 months, while in the second [35] 17% on admission had TSH deficient but none at follow-up.

Endocrine assessment and management of PTHP

There is currently no consensus on who should be screened for PTHP. Despite the lack of a clear-cut relationship between the severity of injury and the incidence of post-TBI pituitary dysfunction [71], risk factors such as the presence of hypotension and hypoxia within the first 24 h after injury and diffuse brain swelling have been identified as increasing the likelihood of PTHP [4]. In their extensive review Tanriverdi et al, have suggested that all TBI patients (regardless of the severity) who need ICU monitoring should be screened during the acute phase and prospectively. They recommend assessing only ACTH deficiency by measuring morning basal cortisol levels during the acute phase on days 1–4 after TBI, and on days 5–10, and in cases of clinical suspicion. There is currently no evidence to support any diagnostic or therapeutic intervention for the acute GH, thyroid hormones or gonadotropins deficiencies, or hyperprolactinemia in the acute phase following TBI [4].

Although adrenal insufficiency (AI) represents the most critical deficit during the early post-traumatic period, definition of AI in the acute post-TBI time, as in any critical situation setting, is often difficult. Critical illness related corticosteroid insufficiency (CIRCI) is characterized by three major pathophysiologic events: dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, altered cortisol metabolism, and variable tissue sensitivity to glucocorticoids. Results of cortisol measurements should not be compared to data from healthy individuals since critically ill patients have higher basal and stimulated cortisol levels. Also, in many occasions the presence of low cortisol binding proteins make serum total cortisol levels unreliable. Moreover, dynamic stimulation with insulin tolerance testing is infeasible and the standard 250-μg or the low 1-μg corticotropin stimulation tests lack standardization in the acute setting [72]. Recently, on behalf of the AACE Adrenal Scientific Committee Hamrahian et al recommended the use of random cortisol and free cortisol levels as the main evaluation tool for adrenal function in critically ill patients. Based on the fact that diurnal variation of cortisol secretion is lost during critical illness, they recommend using a random cortisol of 10 and 15 μg/dl with low binding proteins (albumin ≤ 2.5 gr/dl) and near normal binding proteins (albumin > 2.5 gr/dl) respectively, to trigger glucocorticoid treatment [73]. However, administration of glucocorticoids based on numerical thresholds is not consistently associated with beneficial effects on patients' outcome [72]. Of note, in 2017 the guidelines from the Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) for the diagnosis and management of CIRCI highlighted that the expert task force was unable to reach agreement on a single test that can reliably diagnose CIRCI [74].

Given the challenges inherent in interpreting the results of endocrine tests in acutely ill patients, and the discordant findings in studies of cortisol replacement therapy based on numerical thresholds, the British Neurotrauma Group guidance [75] does not recommend routine testing of pituitary function or measurement of serum/plasma cortisol levels in the acute phase after TBI. Instead, if there is clinical suspicion of cortisol insufficiency (presence of hyponatremia, hypotension or need for higher doses of vasopressors, hypoglycemia), they recommend the initiation immediately of empirical replacement with

hydrocortisone 50 mg 6–8 hourly, intravenously or intramuscularly; or 50–100 mg as an initial intravenous bolus followed by an infusion of 4–8 mg/hour after taking a serum/plasma sample for random cortisol measurement. Weaning of glucocorticoid administration should be based on proper endocrine consultation and assessment. Following the resolution of the acute phase, there is a definite need of reassessing patients in the post-acute period of TBI. In fact, many patients with an anterior pituitary deficiency at the acute post-TBI period are not consistently deficient at 12 months [76]. Therefore, it is recommended that patients should be assessed at 3 months to determine if pituitary hormone deficiencies are present (and to begin replacement therapy if needed), and then at 12 months to determine which deficiencies are permanent [77].

Conclusions

Traumatic brain injury is a common cause of morbidity and mortality particularly among young individuals. The often underdiagnosed complication of post-traumatic hypopituitarism (PTHP) may have a significant role to the morbidity and mortality of these patients. Several alterations of anterior pituitary function in the form of PTHP take place in the acute post-TBI period. The incidence, however, of PTHP remains a matter of debate with considerable variations reported between studies. Although some data suggest that the TBI severity may be a risk factor for PTHP, it is not yet clear which patients are at greatest risk and there is still some controversy regarding whom, when and how to test. In the acute post-traumatic period, acute cortisol deficiency should be diagnosed and managed promptly. Although in the non-critically ill, dynamic tests facilitate the diagnosis of inadequate cortisol secretion, during the acute post-traumatic period assessment and management of cortisol deficiency should only be based on basal cortisol measurements and careful clinical evaluation. There is currently no evidence to support that treatment of acute GH, thyroid hormones or gonadotropins deficiencies may have any benefit. However, a more comprehensive assessment of pituitary function should be undertaken in the post-acute phase, since ongoing pituitary hormone deficiencies may adversely affect the recovery and quality of life of these patients. Last but not least, although only few studies evaluated the anterior pituitary endocrine function in the acute post TBI period in children and adolescents, the diagnosis and management of PTHP is more than crucial for this age group and should not be neglected.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This paper does not contain any studies with human participants or animals performed by any of the authors.

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