

Pituitary functions in the acute phase of traumatic brain injury: Are they related to severity of the injury or mortality?

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Abstract

Primary objective: There are only limited data regarding pituitary functions in the acute phase of traumatic brain injury (TBI) and previous studies have been conducted in only small cohorts of subjects. Therefore we have investigated the pituitary functions in the early acute phase, within 24 hours of trauma, in 104 patients with TBI. Additionally, the relationships between basal pituitary hormones, severity of the trauma and mortality due to trauma were also investigated.

Methods and procedures: One hundred and four TBI patients were included in the study consecutively. All patients underwent basal hormonal evaluation within the first 24 hours of admission. Twenty of 104 patients died during the acute phase.

Main outcomes: Prolactin levels were negatively correlated with the Glasgow coma scale (GCS), cortisol levels were positively correlated with the GCS and cortisol levels were positively correlated with ACTH levels. Additionally there was a significant positive correlation between the total testosterone levels and the GCS in males. Logistic regression analysis revealed that mortality after TBI was unrelated to basal pituitary hormone levels. However age and GCS were significantly related to the mortality. The percentages of pituitary hormone deficiencies were as follows: 3.8% had TSH deficiency, 40.0% had gonadotrophin deficiency, 8.8% had ACTH deficiency and 20.0% had GH deficiency.

Conclusions: Present data clearly demonstrate that pituitary function is disturbed in TBI and the most frequently deficient pituitary hormones were gonadotrophins in the early acute phase of TBI. Basal hormone levels including cortisol, prolactin and total testosterone were related to the severity of the trauma. However there was no relation between basal hormones and mortality due to TBI. Age and GCS were significantly related to mortality.

Keywords: Traumatic brain injury, Glasgow Coma Scale, mild brain injury, pituitary, hypopituitarism

Introduction

Traumatic brain injury (TBI) is a common health problem which is one of the main causes of disability and death among young adults, and newly recognized as a cause of neuroendocrine dysfunction [1]. Although it is commonly stated in textbooks as one of the rare causes of hypopituitarism, recent data have shown that TBI-mediated hypopituitarism could be more frequent [2, 3]. A high occurrence

of neuroendocrine dysfunction particularly in patients with moderate and severe TBI has been reported [3, 4]. However assessment of the pituitary functions in patients suffering from TBI is not a routine procedure in endocrine practice.

Hypopituitarism due to TBI may be partial or complete, and 25–50% of patients who were tested several months and years after head trauma have been demonstrated to have some degrees of pituitary dysfunction [3–7]. Gonadotrophins and

Growth Hormone (GH) are considered as the most common vulnerable pituitary hormones and they seem to be easily affected even after mild TBI [2, 8]. However there is only limited data regarding pituitary functions in the acute phase of TBI and previous studies have been conducted in only small cohorts of subjects [9–11]. The largest study in which pituitary functions have been evaluated in the acute phase in 50 patients with moderate and severe TBI, has been carried out 12 days after head trauma [12].

At least to the best of our knowledge no study has been conducted investigating the basal pituitary hormones in the early acute phase of TBI, within 24 hours of trauma, in a sufficient number of patients and their relations to mortality due to trauma. Therefore we set out to investigate pituitary functions in the early acute phase in 104 patients with TBI. Additionally, the relationships between the basal pituitary hormones, severity of the trauma and mortality due to trauma have been investigated.

Patients and methods

Patients

One hundred and four TBI patients (78 men, 26 women; age 38.8 ± 15.3 , range 16–78 years) who were admitted to the Neurosurgery Intensive Care Unit (NICU) or Neurosurgery Department in Erciyes University Medical School Hospital were included in the study consecutively between 2003–2005. The study was approved by the Local Ethical Committee. Recently we have published the results of 12 month prospective follow-up of TBI patients [7] and these patients were not included in the present study.

The level of consciousness of the patients was evaluated by the same investigator (HS) according to the Glasgow Coma Scale (GCS) as soon as the patient was admitted to the NICU. A score of 13–15 is considered as mild, 9–12 moderate and ≤ 8 severe TBI [13]. None of the patients had a history of any known pituitary disorder and all the patients were off any drug affecting hypothalamo-pituitary function.

The cause of TBI was road traffic accidents in 76.0% of patients, falls in 20.2% of patients and other reasons in 3.8% of patients.

Basal hormonal evaluation in the acute phase

All patients underwent basal hormonal evaluation within the first 24 hours of the admission to the NICU or Neurosurgery Department. Blood samples

were taken between 8.00–9.00 h. Before the blood samples were collected no patients received glucocorticoids, dopamine, ketoconazole or calcium channel blockers. Basal hormone levels including free (f) T₃, fT₄, Thyroid-stimulating hormone (TSH), Prolactin (PRL), cortisol, Adrenocorticotrophic hormone (ACTH), Follicle-stimulating hormone (FSH), LH, IGF-I, GH, and total and free testosterone in men or estradiol in women were measured. Menstrual history was also obtained from women or their relatives. Two of 26 were excluded from the analysis due to the lack of menstrual history and estradiol levels.

- In males, gonadotrophin deficiency was defined by basal total and free testosterone levels below the normal range (total testosterone < 134 ng/dl and free testosterone < 11.5 pg/ml) in the presence of normal or low values of gonadotrophins. In premenopausal women, gonadotrophin deficiency was defined by serum estradiol level less than 11 pg/ml, with the presence of inappropriately low serum gonadotrophin concentration. In postmenopausal women, gonadotrophin levels in the premenopausal range was used to diagnose the deficiency [14, 15].
- TSH deficiency was defined by low serum fT₄ level (< 8 pg/ml) without appropriate elevation in serum TSH [14, 15].
- ACTH deficiency was suggested when basal cortisol level was below 7 μ g/dl [5].
- GH deficiency was suggested in patients who had IGF-I level below 84 ng/ml [16].
- Hyperprolactinemia was defined when basal level higher than normal reference range (male: 2–18 ng/ml, premenopausal women: 2.8–29 ng/ml, postmenopausal women 1.8–20 ng/ml).

Analytical methods

Serum GH levels were measured by using immunoradiometric assay with commercial kit (Diagnostic Systems Laboratories, Webster, Texas, USA) intra-assay and inter-assay coefficients of variation (CV) were 3.1% and 5.9%, respectively and GH standards were calibrated according to the WHO reference standard 88/624. IGF-I level was measured by immunoradiometric assay after formic acid-ethanol extraction (DSL, Webster, Texas, USA); intra-assay and inter-assay CV were 3.4% and 8.2%, respectively.

All the other serum hormones (except TSH, ACTH and estradiol) were measured by using radioimmunoassay (RIA) with following commercial kits; Cortisol (DSL, Webster, Texas, USA; intra-assay and inter-assay CV: 8.4% and

Table I. Comparison of mean age and basal hormone levels in the acute phase between mild, moderate and severe TBI groups.

	Mild TBI group (n = 49)	Moderate TBI group (n = 24)	Severe TBI group (n = 31)
Age	40.7 ± 16.4	37.7 ± 14.2	36.6 ± 14.4
fT3 (pg/ml)	3.0 ± 8.1	2.1 ± 0.63	2.0 ± 0.97
fT4 (pg/ml)	12.2 ± 2.2	13.2 ± 3.9	11.2 ± 3.2 ^a
TSH (mIU/ml)	0.9 ± 0.8	0.99 ± 1.3	1.3 ± 1.2
PRL (ng/ml)	13.3 ± 8.7	14.6 ± 6.1	17.5 ± 16.5 ^a
Cortisol (µg/dl)	21.5 ± 13.7	18.4 ± 5.9	16.7 ± 8.6
ACTH (pg/ml)	36.5 ± 61.6	27.1 ± 29.6	21.7 ± 23.3
FSH (mIU/ml)	5.1 ± 7.4	4.3 ± 8.9	5.1 ± 9.7
LH (mIU/ml)	5.5 ± 6.2	3.8 ± 6.0	3.9 ± 5.1
IGF-I (ng/ml)	182 ± 94	176 ± 119	177 ± 114
GH (µg/l)	6.6 ± 9.5	3.1 ± 6.3	3.8 ± 7.5
Total testosterone ¹ (ng/dl)	203 ± 142	178 ± 161	123 ± 138 ^a
Free testosterone ¹ (pg/ml)	7.8 ± 6.8	5.9 ± 6.1	5.2 ± 4.4

^a $p < 0.05$ vs. mild and moderate TBI group.

¹Testosterone levels were measured only in males.

9.1%, respectively), FSH (ICN Biomedicals, California, USA; intra-assay and inter-assay CV were 2.4% and 7.3%, respectively), LH (ICN Biomedicals California, USA; intra-assay and inter-assay CV were 3.6% and 7.8%, respectively), fT3 (ZenTech, Angleur, Belgium; intra-assay and inter-assay CV were 2.7% and 8.3%, respectively), fT4 (ZenTech, Angleur, Belgium; intra-assay and inter-assay CV were 3.7% and 4.5%, respectively), PRL (ICN Biomedicals, California, USA; intra-assay and inter-assay CV were 7.0% and 8.9%, respectively), total testosterone (Biosource, Nivelles, Belgium; intra-assay and inter-assay CV were 4.6% and 6.2%, respectively), free testosterone (DSL, Webster, Texas, USA; intra-assay and inter-assay CV were 6.2% and 9.7%, respectively), estradiol (Advia centaur system chemiluminescent technology, Bayer, Germany; intra-assay and inter-assay CV were 5.5% and 5.2%, respectively), ACTH-Immunoradiometric assay (IRMA) (DSL, Webster, Texas, USA; intra-assay and inter-assay CV were 2.3% and 8.0%, respectively) and TSH-IRMA (Biosource, Nivelles, Belgium; intra-assay and inter-assay CV were 6.0% and 4.1%, respectively).

Normal reference ranges were as follows: freeT3 (2.2–4.7 pg/ml), freeT4 (8–20 pg/ml), TSH (0.2–4.5 mIU/ml), Prolactin (men: 2–18 ng/ml, premenopausal women: 2.8–29 ng/ml, postmenopausal women: 1.8–20 ng/ml), cortisol (9–23 µg/dl), FSH (men: 1.4–18 mIU/ml, premenopausal women: 2.5–12.5 mIU/ml, postmenopausal women 23–116 mIU/ml), LH (men: 1.5–9.3 mIU/ml, premenopausal women: 1.9–12.5 mIU/ml, postmenopausal women: 16–54 mIU/ml), total

testosterone (men: 134–625 ng/dl), free testosterone (men: 11.5–24.5 pg/ml), estradiol (women: 11–69 pg/ml), ACTH (10–50 pg/ml) and the IGF-I reference ranges (mean – 2 SD, mean + 2 SD) for the relevant ages were (197–476 ng/ml; 18–30 years), (100–494 ng/ml; 30–40 years), (101–303 ng/ml 40–70 years).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 10.0 program. All data were subjected to the Kolmogorov–Smirnov test for normality and are presented as mean ± SD. Normally distributed values between two variables were compared by unpaired *t*-test. More than two variables were compared by using One-Way ANOVA test, and Scheffe test was performed for *post-hoc* analysis. In addition, we used Pearson's correlation analysis to determine whether significant correlations existed between chosen variables. A multifactorial logistic regression model was used to determine which variables independently predicted the development of mortality; $p < 0.05$ was considered significant.

Results

Forty-nine (47.1%) patients had mild (mean GCS: 14.2 ± 0.7), 24 (23.1%) had moderate (mean GCS: 10.9 ± 1.2) and 31 (29.8%) had severe (mean GCS: 5.6 ± 1.4) TBI. 20 (18 male, 2 female) of 104 patients (19.2%) died during the acute phase, and 15 of them had severe TBI.

There was no statistically significant difference in mean age, fT3, TSH, cortisol, ACTH, FSH, LH, IGF-I, GH and free testosterone levels between the patients with mild, moderate and severe TBI. However mean total testosterone level and fT4 was significantly lower and the prolactin level was significantly higher in the patients with severe TBI when compared to mild and moderate TBI groups ($p < 0.05$). The data are shown in Table I.

Prolactin level was available in 97 of 104 patients and 19 (18 male, 1 female) of 97 subjects (18.3%) had hyperprolactinemia. Three of the thyroid function parameters (fT4, fT3, and TSH) were available in 97 of the patients, and 42 of 97 patients (43.3%) had low T3 syndrome (normal fT4, normal TSH and low fT3 levels).

All the possible correlations between GCS and basal hormones and within basal hormones were investigated in all patients. Significant correlations were as follows; prolactin levels were negatively correlated with the GCS ($r = -0.26$, $p = 0.01$), cortisol levels were positively correlated with the GCS ($r = 0.20$, $p = 0.04$) and cortisol levels were positively correlated with ACTH levels ($r = 0.42$,

$p = 0.0001$). Additionally there was a significant positive correlation between the total testosterone levels and the GCS in males ($r = 0.25$, $p = 0.04$), but no significant correlation was found between the estradiol levels and the GCS in females ($r = 0.01$, $p = 0.86$). The significant correlations are summarized in Figure 1(a-d).

Mean age, GCS and basal hormone levels of the patients who died after TBI (no surviving group (NSG); 20 patients) were compared with the living patients (surviving group (SG); 84 patients). There was no significant difference in mean fT3, TSH, PRL cortisol, ACTH, FSH, LH, IGF-I, GH, total testosterone and free testosterone levels between the NSG and SG (data not shown). However age was significantly higher (NSG 48 ± 15.8 , SG 36.7 ± 14.4 ; $p = 0.001$), and mean GCS (NSG 7.4 ± 4.5 , SG 11.7 ± 3.3 ; $p = 0.0001$) and fT4 level (NSG 10.7 ± 1.6 , SG 12.4 ± 3.2 ; $p = 0.017$) were significantly lower in NSG. Logistic regression analysis revealed that mortality after TBI was unrelated to the basal pituitary hormone levels. But age ($p = 0.003$) and GCS ($p = 0.0001$) were significantly related to mortality. When we performed logistic regression analysis

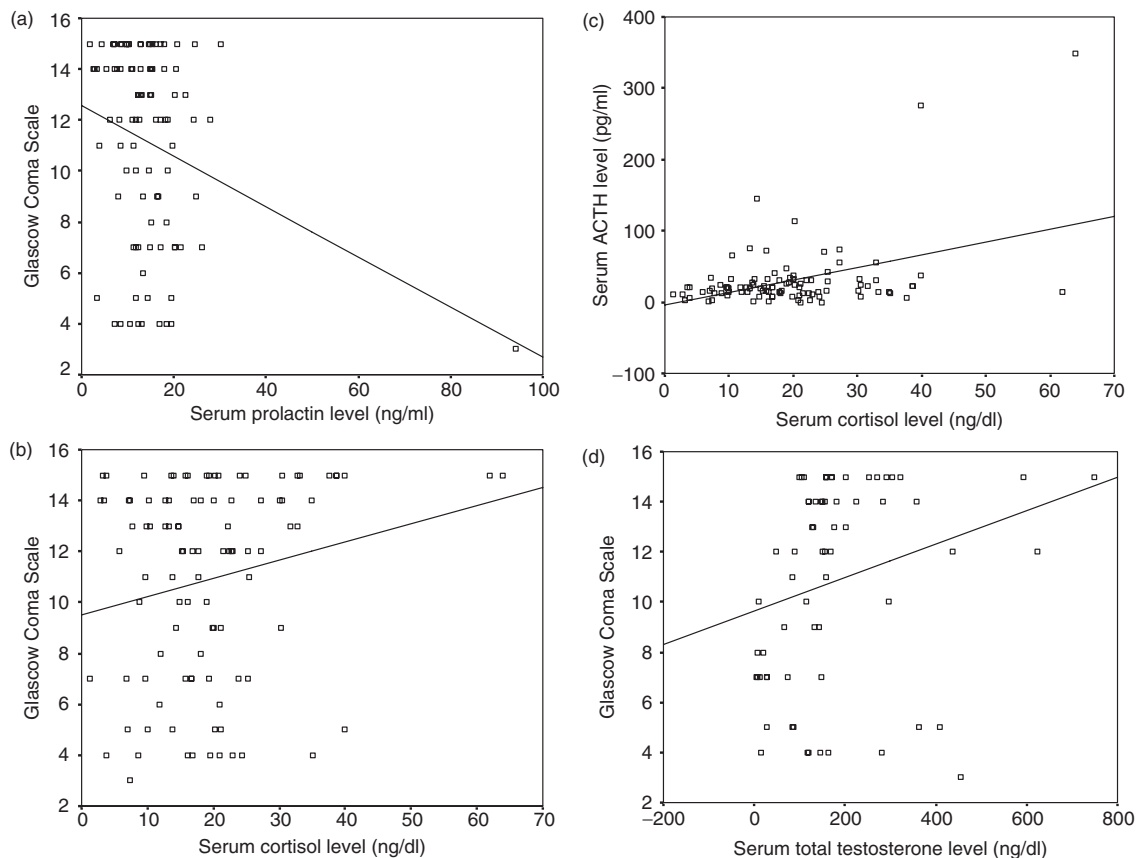


Figure 1. Significant correlations between GCS and serum prolactin level (a), GCS and serum cortisol level (b), serum ACTH and serum cortisol levels (c), and GCS and serum testosterone level (d).

between NSG and SG with mild TBI the results were similar (data not shown).

Based on the criteria summarized in the Methods section, percentages of pituitary hormone deficiencies were as follows: 4 of the 104 patients (3.8%) had TSH deficiency, 38 (29 male, 9 female) of the 95 patients (40.0%) had gonadotrophin (LH/FSH) deficiency. For the whole cohort, the presence of gonadotrophin deficiency was unrelated to hyperprolactinemia ($p=0.75$). Nine of the 102 patients (8.8%) appeared to have ACTH deficiency, and 19 of the 95 patients (20.0%) appeared to have GH deficiency (Figure 2).

Discussion

We demonstrated substantial changes in basal pituitary hormone levels and investigated the possible relations between the pituitary hormonal changes and the severity/mortality of trauma. This is the largest study, to date, evaluating the pituitary functions in the early acute phase after TBI.

The pituitary gland responds to acute traumatic events and several changes in the circulating hormone levels become apparent during the first hours or days after injury, and may continue for the period of acute critical illness [17]. Elevated serum cortisol levels associated with increased ACTH release (probably driven by Corticotropin-releasing factor (CRF), cytokines and noradrenergic system activation) during the initial phase of trauma have been previously reported in patients with mild and moderate TBI [18, 19]. Additionally a positive correlation between the severity of the injury and cortisol concentrations has been shown in patients with mild or moderate TBI, but not in those with severe injury [18]. In contrast primary or secondary adrenal failure has been shown in 15% of patients with moderate to severe injury, 7–60 days after TBI,

by using the CRH and low-dose ACTH tests [20]. In the present study cortisol levels were positively correlated with ACTH levels implying the centrally activated hypothalamo-pituitary adrenal (HPA)-axis during the acute phase of TBI. Additionally there was a negative correlation between the cortisol levels and the severity of the trauma suggesting that increased severity of the trauma results impaired HPA axis response. Severe trauma may give rise to more hypothalamic or pituitary damage, and results in blunted HPA-axis response to stress. The limitation of the present study was the investigation of GH and cortisol deficiencies by basal hormone levels. We did not perform any stimulation tests for the diagnosis of GH and cortisol deficiencies during the early acute phase because of two main reasons. It is technically difficult to perform a test at ICU conditions within 24 hours of TBI, and the diagnosis of cortisol and GH deficiency was challenging in acute severe illness due to the difficulties in selecting a reliable stimulation test and universally accepted cut-off levels [6, 21].

Previous studies have clearly demonstrated that testosterone levels in males and estrogen levels in females significantly fall within the first 24 hours following TBI and remain lowered for 7–10 days. In this phase testosterone concentration has been shown to be negatively correlated with the severity of injury [22, 23]. Consistent with previous studies mean total testosterone level in male patients was significantly lower in the severe TBI group when compared to mild and moderate groups, and total testosterone levels were negatively correlated with the severity of the injury in the present study. There was no any significant correlation between the estradiol levels and the GCS which may be due to the low number of female patients. However it is still unknown whether there is a gender difference in endocrine response to trauma.

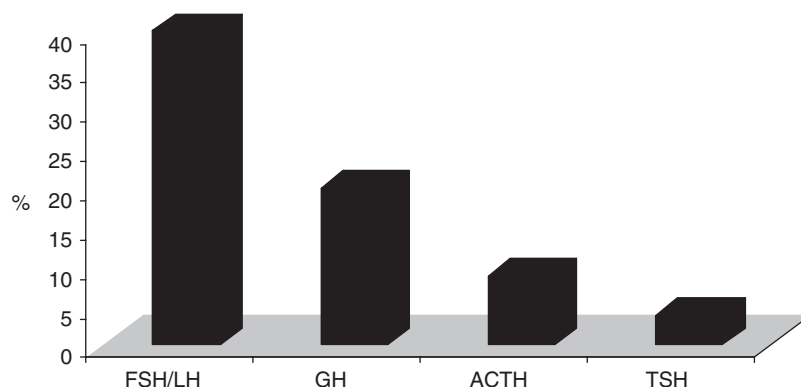


Figure 2. Percentages of the pituitary hormone deficiencies in the early acute phase of TBI.

In the acute phase of TBI hyperprolactinemia has been reported in more than 50% of the patients who had moderate or severe injury [12, 24]. A positive correlation between the severity of the trauma and the prolactin levels has been demonstrated in previous studies [12, 24]. In this study hyperprolactinemia was found in 18.3% of the subjects. This lower prevalence of hyperprolactinemia in this study is probably related to the severity of TBI, because most of our patients had mild trauma and variable prevalences of hyperprolactinemia in different studies may be related to the severity of TBI. Stalk lesions or hypothalamic lesions are generally related to hyperprolactinemia. Thus the normal serum prolactin levels in most of our patients were suggestive of a pituitary lesion. Therefore it is tempting to speculate that mild injuries may generally affect pituitary, but severe injuries may affect the stalk and hypothalamus. Future experimental models are warranted to understand the relationship between severity of the trauma and the localization of the lesion.

Acute illness or trauma induces several changes in thyroid hormone levels within hours [21]. Presence of low T3 syndrome and recovery over weeks have been demonstrated in a few studies [9, 25]. Only the study by Chiolero et al. has shown that serum TSH concentrations were significantly lower in the patient group relative to controls in the early phase after injury, although fT4 levels were similar [9]. In the present study we found the percentages of low T3 syndrome substantially high (43.3%) which may be partly due to decreased T4 conversion to T3 and/or increased thyroid hormone turnover [21].

Twenty patients died in NICU, and when compared with surviving patients the mean age was significantly higher, GCS and fT4 were significantly lower. But we could not find any relation between basal pituitary hormone levels and mortality. The only significant variables related to mortality were increased age and low GCS. Although there are not enough data regarding the relation between pituitary hormones and the mortality, extremely high cortisol levels have been previously reported as one of the factors in the prediction of fatal outcome after head injury [26]. It has recently been shown that GCS and age are independent early predictors of mortality and morbidity after acute TBI. In contrast, the increment in cortisol does not add any information to outcome prediction [20, 27].

Based on basal hormone levels we found the percentages of TSH, gonadotrophin, ACTH and GH deficiencies as 3.8%, 40.0%, 8.8% and 20.0%, respectively. In a recent study Agha et al. have evaluated 50 consecutive patients in the acute phase (median of 12 days, range 7–20 days) of TBI. The majority of their patients (64%) had severe

head injury and they had been tested at a median of 12 days following injury. They tested GH and cortisol deficiency by glucagon test and other hormone deficiencies by basal hormones. Pituitary hormone deficiencies have been found as follows; GH (18%), cortisol (16%), gonadotrophin (80%) and TSH (2%) [12]. In both studies the most common deficient hormones were gonadotrophins and the least was TSH deficiency. In that study the percentage of gonadotrophin deficiency was significantly higher than that found in our patient group probably because most of the patients (51.3%) in the present study had mild injury. However it is not clear whether the reported hormone deficiencies are secondary to structural hypothalamic-pituitary injury and permanent, or if they reflect an adaptive mechanism to acute illness. The limitations of the present study were as follows: this was not a blinded study and a control group could not be included.

There are several mechanisms for hypothalamo-pituitary dysfunction due to TBI including hypoxic insult or direct mechanical injury to the hypothalamus, pituitary stalk, or the pituitary gland; compression from hemorrhage, edema, or increased intracranial pressure; and vascular injury to the hypothalamus or the pituitary gland [3, 28, 29]. Based on autopsy results in patients who died from TBI, there was an evidence of injury to the hypothalamus, the pituitary gland or the pituitary stalk in 26–86% of the patients [30–32]. Rotational acceleration-deceleration can stimulate shearing injury of axons and it is commonly seen in midline structures of the brain. This may represent a possible mechanism of hypothalamic pituitary dysfunction after TBI [33]. Nevertheless the exact mechanisms of TBI at molecular and cytokine level remain to be clarified.

In conclusion, our data clearly demonstrate that pituitary function is disturbed in TBI and the most common deficient pituitary hormones were gonadotrophins in the early acute phase of TBI. Several basal hormones including cortisol, prolactin and total testosterone were related to the severity of the trauma. However we could not demonstrate any relation between the basal pituitary hormones and mortality due to TBI. Future clinical and experimental studies are warranted to uncover the mechanisms and the physiological relevance of these hormonal changes after acute TBI.

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