Neuroendocrine Changes are common during the acute Phase of Traumatic Brain Injury and Subarachnoid Hemorrhage

Authors:
1. Petur Sigurjonsson MD Msc., Landspitali University Hospital, Department of Anesthesia and Intensive Care, Reykjavik, Iceland
2. Asta Dogg Jonasdottir MD Msc., Landspitali University Hospital, Department of Endocrinology, Reykjavik, Iceland
3. Ingvar H Olafsson MD, Landspitali University Hospital Department of Neurosurgery, Reykjavik, Iceland
4. Sigurbergur Karason MD, PhD, professor, Landspitali University Hospital Department of Anesthesia and Intensive Care, Reykjavik, Iceland and Faculty of Medicine, University of Iceland
5. Gudmundur Sighorsson MD Msc PhD, Landspitali University Hospital Department of Clinical Chemistry, Reykjavik, Iceland
6. Helga A Sigurjonsdottir MD, PhD, professor, Landspitali University Hospital, Department of Medicine, Reykjavik, Iceland and Faculty of Medicine, University of Iceland.

*petursigurjonsson@gmail.com

ABSTRACT

Background and aims of the study: Traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH) can cause death and long-term morbidity. Studies indicate that both TBI and SAH may affect pituitary function in both the acute and the chronic phase. The aims of this study were firstly to evaluate the nature of neuroendocrine changes in the acute phase of moderate and severe TBI and all SAH, to evaluate association between neuroendocrine disturbance and indicators of severity of insult as well as hypotension, desaturation and anemia and to evaluated the incidence of neuroendocrine changes after moderate and severe TBI and SAH in the acute phase. Purpose: To explore neuroendocrine disturbances in moderate traumatic brain injury (mTBI), severe TBI (sTBI) and subarachnoid hemorrhage (SAH) in the acute phase.

Methods: The study was a prospective single-center study. Anterior hypothalamic-pituitary (HP) hormone axis were assessed on admission (day 0) with baseline hormone levels and on day 6 post insult with baseline hormone levels and a Synacthen test. From patient charts we recorded for all patients GCS, APACHEII score, length of ICU stay, pupil dilatation, documented hypotension, desaturation and hemoglobin value <80 g/dL. Hunt and Hess grade for SAH group and Injury severity score for TBI group. S100b was measured in all patients on admission. We included 21 TBI patient, 6 moderate TBI and 15 severe TBI, and 19 SAH patients. Anterior hypothalamic-pituitary (HP) hormone axis were assessed on day 0 and 6 post insult in Twenty-one TBI patient and 19 SAH patients.

Results: HP-adrenal axis: The TBI group had significantly lower mean cortisol than the SAH group on day 0, 23.8% of TBI patients had low cortisol and 0% of SAH patients. On day 6, one patient in each group had low cortisol, 6.7% of TBI and 9.1% of SAH. HP-gonadal axis: In males on day 0, 52.9% of TBI patients and 57.1% of SAH patients had suppressed HP-gonadal axis and on day 6, 84.6% of TBI patients and 90% of SAH patients. There was a greater suppression of LH/FSH in the TBI group. HP-thyroid axis: Only one TBI patient (5.9%) had secondary hypothyroidism on day 6. HP-somatotroph axis: On day 0, 52.4% of TBI patients and 35.7% of SAH patients had low IGF-1. On day 6 all but one TBI patient (5.9%) had normalized their IGF-1 but 25% of SAH patients still had low IGF-1. In general, when evaluating association there seemed to more suppression of the hypothalamic-pituitary (HP) gonadal and thyroid axis with more severe insult and adequately more activation of the hypothalamic-pituitary adrenal axis.

Conclusion: Neuroendocrine disturbances in the acute phase of TBI and SAH are common and seem to differ between the two groups. The clinical significance of these disturbances is uncertain.

Keywords: Traumatic brain injury, Subarachnoid hemorrhage, Neuroendocrine disturbances, hormonal change.
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Introduction:
Traumatic brain injury (TBI) is a leading cause for permanent disability and death among young people. Subarachnoid hemorrhage (SAH) accounts for 5% of all strokes and causes permanent disability.

During the last decades studies have yielded conflicting results regarding the neuroendocrine response in the acute phase of TBI. Reported prevalence of ACTH/cortisol deficiency in TBI patients (TBIp) varies between 4-78% and 0-42% in SAH patients (SAHp). The prevalence of thyroid hormone deficiency has been reported as 2-52% for TBIp and 0-23% for SAHp and the prevalence of somatotrophic insufficiency has been reported as 18-41% in TBIp and 12-23% in SAHp. Disturbances in the gonadotroph axis in the acute phase of TBI and SAH is common with reported incidence as high as 100% in male patients with SAH. Different results in previous studies can possibly be explained by differences in patient selection, methodology, timing of assessment and effect of ICU treatment. Appropriate basal levels of hormones are not yet defined in the critically ill. Commonly used endocrine tests should be used with caution and dynamic tests are often unsuitable due to slow turnaround or issues with safety.

The aims of this study were to explore neuroendocrine disturbances and identify possible prognostic factors during the acute phase in moderate TBI (mTBI), severe TBI (sTBI) and SAH in an Icelandic cohort. The study is prospective and nationwide, as all SAH and severe TBI and most moderate TBI are transferred and treated at the Landspitali University Hospital which houses the only Neurosurgery department in the country. Patients included were even prospectively followed and underwent endocrinological assessment 3 and 12 months post insult, published earlier.

Materials and methods
Subjects
During 12 months, patients admitted to The National University Hospital of Iceland with moderate and severe TBI or SAH were prospectively included. Inclusion criteria for TBIp was age 18-70 years and moderate (mTBIp) or severe TBI (sTBIp), judged by post resuscitation Glasgow coma score, <9 or 9-12 respectively. All patients with SAH were included with no age or GCS criteria. LUH houses the only neurosurgery department in Iceland covering a region of approximately 318,000 inhabitants at the time of the study.

Twenty-one TBIp and 19 SAHp were included. TBI was caused by traffic accidents (car, bicycle and pedestrian) in 7 patients, fall in 6 patients, assault in 4 patients and construction working accident in 4 patients. One, sTBIp, died before day 6 and one mTBIp and 2 sTBIp were discharged from the hospital before day 6 and did not attend to the offered follow-up. One sTBIp missed testing at day 6 but was tested on day 9 post trauma. Those results were analyzed with the day 6 result. Nine TBIp were intoxicated by alcohol at the time of trauma.

SAH diagnosis was confirmed on a CT scan in all of the patients. Five patients were included at later stages as these patients did not seek medical help until days after the beginning of symptoms. Day 0 was defined when the symptoms began. Three SAHp died before day 6. Three SAHp were tested on day 8, 10 and 14 respectively as they were not discharged until days after the beginning of symptoms.

Anterior pituitary assessment:
Anterior pituitary function was assessed on or within hours of admission, as soon as informed consent had been acquired, by analyzing serum levels of cortisol (s-cortisol), insulin like growth factor 1 (s-IGF-1), thyroid stimulating hormone (s-TSH), free thyroxine 4 (s-FT4), prolactin (s-PRL), luteinizng hormone (s-LH), follicle stimulating hormone (s-FSH), total testosterone (in men) and oestradiol and progesterone (in women) as well as plasma levels of adrenocorticotropic hormone (p-ACTH). On the 6th day after the insult anterior pituitary function was assessed again by repeating the above mentioned hormone level measurements. Blood samples were drawn in the morning as close to 8 am as possible and additionally a Synacthen test (SynTest) was performed. SynTest was performed by measuring s-cortisol and p-ACTH at baseline followed by injection of tetracosactrin (Synacthen) 250 mcg iv. S-cortisol was measured 30 and 60 min after the injection.

In accordance with recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill (CIRCI) adult patients: consensus statements from an international task force by the American College of Critical Care, cortisol deficiency was defined as a s-cortisol value of <276 nmol/L or an increase of <248 nmol/L after SynTest. Suggested somatotropin deficiency was defined as subnormal age- and gender related IGF-1 value. Thyrotropin deficiency was defined as subnormal s-FT4 with inappropriately low serum levels of TSH. Gonadotropin deficiency was defined as subnormal s-testosterone (in men) and inappropriately low s-LH and s-FSH.

Serum levels of S100b was analyzed on arrival.
Analytic methods
S-fT4, s-TSH, s-progesterone, s-estradiol, s-PRL, s-cortisol and S100b were analyzed using Electrochemiluminescence immunoassay (Modular Analytics E170, Roche, GmbH). GH was analyzed using a solid-phase, two-site chemiluminescent immunometric assay (IMMULITE/IMMULITE 1000, Siemens). S-IGF-1 was analyzed using a solid-phase, enzyme labeled chemiluminescent immunometric assay (IMMULITE/IMMULITE 1000, Siemens) and p-ACTH using a solid-phase, two site sequential chemiluminescent immunometric assay (IMMULITE/IMMULITE 1000, Siemens).

The method for analyzing the s-GH was changed during the study period. Thus s-GH levels were measured with IMMULITE/IMMULITE 1000 Growth Hormone, Siemens and IMMULITE/IMMULITE 1000 Growth hormone (Recombinant 98/574), Siemens.

From patients chart we recorded the first post-resuscitation GCS for all patients, Hunt and Hess grade for SAHp based on neurological examination at arrival, injury severity score for TBIp, an established medical score to assess trauma severity 17, APACHEII score (Acute Physiology and Chronic Health Evaluation II) for all patients, a severity-of-disease classification system 18, length of ICU stay, the occurrence of pupil dilatation, the occurrence of documented serum haemoglobin level (Hb) below 80 g/dl and the occurrence of hypotension defined as a recorded systolic blood pressure (SBP) <90 mmHg and hypoxia defined as a recorded SpO2<90% either during the first hour post insult or during hours 1-24.

Statistics
All statistical analyses were performed by using IBM SPSS statistics version 20. Continuous data is presented as median (range) and mean (± SEM).

Normality was tested using Shapiro-Walk. Only part of our data had a normal distribution thus non-parametric tests were used for all. To compare differences in hormone values within each group at different time points Wilcoxon signed rank test was used. To compare differences in continuous variables between TBI and SAH groups Mann-Whitney U test was used. To compare differences in nominal variables between TBI and SAH groups Fischer exact test was used. To compare difference in TBIp and SAHp that is number of individuals with low, normal and high hormones, categorical variable with three categories, Kruskal-Wallis H was used. Correlation analyses were done using Spearmans rho for categorical and continuous variables. Statistical significance was accepted at p < 0.05.

Results
The TBI group was significantly younger with a median age of 34 years (range 47 years) compared to the SAH group with a median age of 56 years (range 55 years), p<0.001. GCS was lower in the TBI group with the median of 7 (range 9) compared to 14 (range 12) in the SAH group, p=0.003. No significant difference was found in APACHE II, length of ICU stay, dilatation of pupil, hypotension, hypoxia or anemia between the groups.

Mean and median hormone values on admission and on day 6 for the TBI and SAH groups are presented in Table 1 as well as comparison between the groups. Proportion of patients with low, normal or high hormone values on admission and day 6 are presented in Figure 1a and 1b.
### Reference range

<table>
<thead>
<tr>
<th>Reference range</th>
<th>Day 0 TBI patients</th>
<th>N</th>
<th>Day 0 SAH patients</th>
<th>N</th>
<th>Day 6 TBI patients</th>
<th>N</th>
<th>Day 6 SAH patients</th>
<th>N</th>
<th>p-value TBI d0 vs d6</th>
<th>p-value SAH d0 vs d6</th>
<th>p-value TBI d0 vs SAH d0</th>
<th>p-value TBI d6 vs SAH d6</th>
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<tbody>
<tr>
<td>TSH = thyroid stimulating hormone, fT4 = free thyroxine, LH = luteinizing hormone, FSH = follicle stimulating hormone, ACTH = adrenocorticotrophic hormone, IGF-1 = Insulin growth factor 1, ns = non significant</td>
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</table>

#### Table 1. Mean and median hormone values on admission and day 6, TBI group

Comparison done with Wilcoxon signed rank test thus values are paired and excluded if missing value. Data is presented as mean±SEM and median (range).

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**Figure 1a** Proportion of both TBI and SAH patients on admission with low, normal or high hormone values. TSH = thyroid stimulating hormone, fT4 = free thyroxine 4, LH = luteinizing hormone, FSH = follicle stimulating hormone, ACTH = adrenocorticotrhop hormone, IGF-1 = Insulin like growth factor 1

**Figure 1b** Proportion of both TBI and SAH patients on day 6 with low, normal or high hormone values. TSH = thyroid stimulating hormone, fT4 = free thyroxine 4, LH = luteinizing hormone, FSH = follicle stimulating hormone, ACTH = adrenocorticotrhop hormone, IGF-1 = Insulin like growth factor 1

**Hypothalamic-pituitary-adrenal axis**
One SAHp had received corticosteroids before blood samples were drawn on admission. Two TBIp and 7 SAHp received treatment with corticosteroids the first 6 days, decided by the treated physician. These patients are excluded in calculations although mentioned below.
On admission 5 of 21 (23.8%) TBIp had cortisol deficiency, s-cortisol <276 nmol/L and concomitant low p-ACTH levels, one patient had plasma ACTH 11 ng/L and the other four levels below detectable value (<10 ng/L). On day 6, 1 of 15 (6.67%) TBIp had s-cortisol 155 nmol/L and p-ACTH <10 ng/L. That patient had a normal response on the SynTest. Two patients had received treatment with corticosteroids. One of them had received treatment with dexamethasone and had s-cortisol of 10 nmol/L and ACTH <10 ng/L and failed the SynTest, with a maximal response of 356 nmol/L. He was treated with corticosteroids and retested on day 19 and then had a normal SynTest. The other patient was treated with cortisone, had normal s-cortisol and a normal response on the SynTests. Two TBIp with high s-cortisol were not tested with a SynTest on day 6. All other TBIp underwent a SynTest and showed a normal response.

Only 1 of 14 (7.1%) SAHp had low s-cortisol on the first blood sample and that patient had already received corticosteroids complicating interpretation thus no SAHp had definite cortisol deficiency. On day 6, 1 of 11 SAHp (9.1%) had s-cortisol of 270 nmol/L and p-ACTH 48 ng/L and then showed a normal response on SynTest.

**Hypothalamic-pituitary gonadal axis**

Testosterone was the most commonly affected hormone in both TBIp and SAHp. On admission, 9 of 17 (52.9%) male TBIp had low s-testosterone. Of these patients two had concomitant low s-LH and s-FSH and two had s-LH and s-FSH in the lower normal range. On day 6, 11 of 13 (84.6%) male TBIp had low s-testosterone, 4 (30.8%) had concomitant low s-LH and s-FSH, 2 had low s-LH, and s-FSH in the lower normal range, 2 with low s-FSH, and s-LH in the lower normal range.

On admission 4 of 7 (57.1%) male SAHp had low s-testosterone but all had normal or high of s-LH and s-FSH. On day 6, 9 of 10 (90.0%) male SAHp had low s-testosterone of which two had concomitantly inappropriately low s-LH and s-FSH (20%).

Gonadal hormone levels for females are not presented due to uncertainty of where in the menstrual cycle the women were or whether they were pre- or postmenopausal making any interpretation of the results unreliable.

**Hypothalamic-pituitary lactotrophic axis**

S-Prolactin showed similar trends in both TBI and SAH group with high levels on admission and a trend to decreasing levels on day 6.

On admission, 7 of the 21 (33.3%) TBIp had abnormally high s-prolactin. On day 6, 5 of 17 (29.4%) TBIp had abnormally high and 1 of 17 patients (5.9%) abnormally low s-prolactin.

On admission, 4 of 14 (28.6%) SAHp had abnormally high s-prolactin and 1 of 4 patients (7.1%) had abnormally low s-prolactin. On day 6, 2 of 19 (10.5%) SAHp had abnormally high s-prolactin and 1 of 19 (5.3%) SAHp had abnormally low s-prolactin.

**Hypothalamic-pituitary thyrotrophic axis**

In the TBI group, 3 of the 21 patients (14.3%) had abnormal thyroid tests on admission and 2 of 17 (11.8%) on day 6. One TBIp had values compatible with primary hypothyroidism on admission with high s-TSH and low s-fT4, not having diagnosed hypothyroidism earlier, and on day 6 s-fT4 was within reference range but s-TSH still high. Another patient had low s-fT4 with normal s-TSH on admission but normal levels on day 6. The third patient had high s-TSH with low s-fT4 on admission and on day 6 low s-fT4 with low s-TSH compatible with secondary hypothyroidism. That patient had severe TBI and later died.

In the SAH group 2 of the 14 patients (14.3%) had abnormal thyroid tests on admission and 2 of 16 (12.5%) on day 6. One patient had high s-TSH with normal s-fT4 on admission but normal values on day 6. One patient had low s-fT4 with normal s-TSH on admission but on day 6 normal s-fT4 with high s-TSH. The third patient had normal values on admission but on day 6 low s-TSH with normal s-fT4.

**Hypothalamic-pituitary somatotrophic axis**

Because of age related reference range and the demographic differences in the TBI and SAH group comparison of mean s-IGF-1 is not feasible. There was however a difference in changes in s-IGF-1 between groups as demonstrated in figure 2a and 2b. There was a significant difference between the groups in the proportion of patients with s-IGF-1 out of normal range on day 6, with lower proportion of low s-IGF-1 and higher proportion with high s-IGF-1 in the TBI group as shown in figure 1b.

On admission 11 of 21 (52.4%) TBIp had abnormally low s-IGF-1. On day 6 only 1 of 17 (5.9%) TBIp had low s-IGF-1, the same patient had low levels on admission. Three patients with normal levels on admission had abnormally high s-IGF-1 on day 6.

On admission 5 of 14 (35.7%) SAHp had abnormally low s-IGF-1. On day 6, 4 of 16 (25.0%) SAHp had low s-IGF-1, three of the patients with low levels on admission still had low s-IGF-1 on day 6 and one patient included after
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admission. Two patients with low levels on admission had normalized their s-IGF-1 on day 6.

Figure 2a

![IGF-1 - TBI group](image)

Figure 2b Changes in Insulin like growth factor 1 (IGF-1) in the SAH group from admission to day 6, each line represents one patient.
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Overview of significant correlation between variables used as indicators of severity and hormone values, on admission and day 6, is provided in table 2.

**Correlations between hormone values and indicators of severity**

Overview of significant differences in hormone values of TBIp or SAHp with documented occurrence of pupil dilatation, Hb < 80 g/dl, hypotension or hypoxia during the first hour post insult or hours 2-24 post insult is presented in table 3.

**Table 2** Overview of significant correlation between variables, indicators of severity, and hormone values in TBI patients

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Hormone</th>
<th>Spearman’s rho</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>GCS</td>
<td>TSH day 6</td>
<td>0.547</td>
<td>0.023</td>
</tr>
<tr>
<td>GCS</td>
<td>fT4 day 0</td>
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<td>0.009</td>
</tr>
<tr>
<td>GCS</td>
<td>FSH day 0</td>
<td>-0.594</td>
<td>0.012</td>
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<tr>
<td>GCS</td>
<td>testosterone day 0</td>
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<td>0.021</td>
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<tr>
<td>ISS</td>
<td>fT4 day 0</td>
<td>-0.484</td>
<td>0.026</td>
</tr>
<tr>
<td>ISS</td>
<td>cortisol day 6</td>
<td>0.561</td>
<td>0.030</td>
</tr>
<tr>
<td>S100b</td>
<td>cortisol day 0</td>
<td>0.538</td>
<td>0.012</td>
</tr>
</tbody>
</table>

**Table 3**: Significant differences in hormone values grouping TBI whether dilatation of pupil or ischemic event occurred or not. Hormone values and S100b presented as mean ± SEM and median (range). TSH = thyroid stimulating hormone, ACTH = adrenocorticotrophic hormone, Hb = hemoglobin.
Discussions
In this prospective study we found neuroendocrine disturbances, to be common in the acute phase of both TBI and SAH that also differed between the groups. A good predictive factor for neuroendocrine disturbance was not identified.

Hypothalamic-pituitary adrenal axis
Diagnosing a clinically relevant cortisol deficiency in the acute settings of any critical care patient is challenging but the most important hormone deficiency to diagnose. Relying solely on SynTest is not recommended since the adrenals may, still respond up to 6 weeks after pituitary failure and even show a response to the high dose of Synacthen despite being resistant to endogenous ACTH. In this study all patients had a normal response on SynTest independent of the s-cortisol level. Furthermore the cut-off value for the diagnosis of CIRCI and dosage of supplemental hydrocortisone is still much debated.

The reported incidence of corticotroph dysfunction in TBI and SAH is inconsistent that can partly be explained by different methodology and definitions. There are studies showing both higher and lower incidence compared to our results for the TBI group. Our results for the TBI group are in line with the study of Klein Dienst et al using similar definitions to ours. Tanriverdi et al used even more stringent baseline cortisol value and found lower incidence. We found no SAHp with corticotroph dysfunction on admission and only one patient on day 6. This is comparable with results from Poll et al but less than others have reported.

There is conflicting data on the association between cortisol levels in the acute phase of TBI and clinical outcome with both better and worse outcome reported. Cortisol deficiency and abnormality in diurnal cycle of cortisol in SAHp are associated with worse outcome. The association between cortisol and worse outcome may possibly be explained by the fact that patients with lower levels of cortisol have had a more severe insult.

The association we found between s-cortisol and p-ACTH, S100b, injury severity score (ISS) and hypotension (see table 3) seems like an adequate response with higher cortisol levels in more severely injured patients.

The difference in s-cortisol between TBIp and SAHp on admission may be explained by TBIp inadequately responding thus having a relative hypothalamic-pituitary adrenal insufficiency or SAH producing a stronger sympathetic response. The difference could even lie in different treatment. The TBI group had significantly lower GCS and thus are more likely to be sedated and intubated. High dose propofol and thiopentonal has been shown to be associated with lower cortisol levels.

Treatment with corticoids in the acute phase of brain injury should be differentiated into replacement therapy for corticosteroid insufficiency and pharmacological treatment as a part of neuroprotective treatment. In the CRASH trial TBIp received supra-physiological doses of methylprednisolone. The trial constitutes 80% of the patients used in a Cochrane review which showed an increase in mortality with corticosteroid treatment in the acute phase of TBI. A Cochrane review on corticosteroid treatment in the acute phase of SAH was inconclusive.

It is clear from the discussions above that previous studies show conflicting results and the field is complicated by factors such as intensive care treatment, different definitions and time of testing. Furthermore, our results imply that there is greater suppression of the hypothalamic-pituitary (HP) axis in TBI compared to SAH patients and relatively common for TBI patients to have cortisol values suggestive of CIRCI. Diagnosing and treating true HP-adrenal deficiency is life saving and there is much need for further studies in this field.

Hypothalamic-pituitary gonadal and lactotroph axis:
In line with previous studies the HP- gonadal axis was the most commonly affected axis with majority of male patients having low testosterone. This is considered an adaptive response where the body is reducing energy consumption and conserving substrates for more vital functions.

Stronger suppression at the pituitary level in the TBI group compared to the SAH may indicate difference in the mechanism of neuroendocrine disturbances in these two groups. This might be explained by differences in the primary injury in TBI vs SAH.

We found a strong negative correlation between s-testosterone on day 6, in the SAH group and length of ICU stay which is in line with previous studies showing more suppression with increased severity.

As expected after trauma, prolactin levels were generally high on day 0.

Hypothalamic-pituitary thyroid axis
Our results are in line with previous studies with only a small portion of patients in both the TBI and SAH groups with s-fT4 and s-TSH below reference ranges. Other studies reporting higher...
prevalence of HP-thyroid disturbances have mainly reported low T3 syndrome which was not evaluated in our study 9,13,29.

We did find a significant decrease in s-FT4 in the SAH group between admission and day 6 which is in line with previous studies which have shown a reduction in both s-FT4 and s-TSH with time in TBI and acute illness 22,31.

The association we found between s-TSH and GCS, s-FT4 and ISS in the TBI group and s-FT4 and GCS, Hunt and Hess score, APACHE1 and length of ICU stay in the SAH group is in line with previous studies suggesting an association between the suppression of the HP-thyroid axis in more severe illness and possibly an adaptive response 11,22,31,32. Surprisingly, we found a negative correlation between s-FT4 on day 0 and GCS which is conflicting with the above and difficult to explain.

Hypothalamic-pituitary somatotroph axis
Our results on suggested somatotropin deficiency in the TBI group are in accordance with previous studies 22,29. However, Kleindienst et al did not show as much restoration of s-IGF-1 on day 7 in a group of TBI patients. Regarding the SAH group previous studies have shown similar prevalence of low s-IGF-1 9,28. Bendel et al measured s-IGF-1 on days 1-7 post SAH, 77% had low s-IGF-1 on day 1 and 76% had low s-IGF-1 on day 7. They even reported association between lower s-IGF-1 and poorer quality of life, assessed by HRQol 33. Difference in the insult per se in TBI and SAH or different treatments can possibly explain the difference seen in changes in s-IGF-1 over time in our study. Causes for low s-IGF-1 include growth hormone insufficiency, decreased liver production and stress following critical illness 33.

Further studies on both the behavior and role of IGF-1 in both TBI and SAH are needed.

Strengths and limitations of the study:
The strength of our study is that there is only one neurosurgical department in Iceland serving all severe TBI and SAH patients and most moderate TBI patients. Our study, a single-center prospective study, is thus a complete study on a national level that by our knowledge is novel.

An important limitation of the study is the small number of subjects. Also, the timing of the first blood samples did vary, depending what time of the day patients presented making the interpretation difficult. The study design was not intended for a comparison between the TBI and SAH group as in a case-control study. Further, the study design did not include interference of the treatment post insult as interfering with that treatment could not only be wrong but even hazardous. This might affect the results, as patients received different treatment post insult as symptomatic treatment both on the ICU and follow up ward was given as usual.

Conclusion:
We conclude that neuroendocrine disturbances are common in the acute phase of TBI and SAH but to a different extent. There is greater suppression of the HP-adrenal axis in TBI compared to SAH patients, greater suppression of the HP-gonadal axis at the pituitary level in the TBI group compared to the SAH group and lower IGF-1 levels on day 6 in the SAH group compared to the TBI group. This may indicate a different causative mechanism for hormonal disturbance in the two groups.

We believe clinicians should evaluate the HP-adrenal axis on indication such as circulatory instability in the acute phase of TBI and SAH as treatment with hydrocortisone may be life-saving. The clinical significance of the disturbances in other than the HP-adrenal axis, whether adaptive or maladaptive, is uncertain. Routine evaluation of other hormonal axis during the acute phase of TBI or SAH might indicate a need for further follow up in the chronic phase of TBI or SAH insult.

Statements and Declarations:
The authors declare that they have no conflict of interest. This work was supported by the The Landspitali University Hospital Research Fund. The study was approved by the Ethics Committee of LUH (no 84/2008) and The Icelandic Data Protection Authority (no 2008120911pJ/---). All participants or their closest of kin gave their written consent after receiving oral and written information about the study.

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