Neuroendocrine changes in the acute phase of traumatic brain injury and subarachnoid hemorrhage

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Thesis for the degree of Master of Science
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HÁSKÓLI ÍSLANDS

Hormónabreytingar í bráðafasa sjúklinga með höfuðáverka eða innanskúmsblæðingu

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Ritgerð til meistaragráðu í líf- og læknavísindum

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Ágrip

Inngangur: Höfuðáverkar (HÁ) og innanskúmsblæðingar (ISB) valda dauða og varanlegri fötlun. Rannsóknir benda til að HÁ og ISB hafi áhrif á starfsemi fremri heiladingulsins í bæði bráða- og síðfasa TBI og SAH. Markmið rannsóknarinnar voru að meta eðli hormónabreytinga í bráðafasa miðlungs og alvarlegra HÁ og allra ISB. Að meta tengsl hormónabreytinga og alvarleika áfalls sem og lækkunar í blóðþrýstingi, súrefnismettun og blóðleysi.

Efni og aðferðir: Rannsóknin var framsýn og framkvæmd á einni stofnun. Hormónaöxlar fremri heiladinguls voru metnir við innlögn (dag 0) með hormónamælingum og 6 dögum eftir áfall með hormónamælingum og Synacthen prófi. Úr sjúkraskrám bæði HÁ og ISB sjúklinga (sjkl.) var skráð GCS, APACHEII skor, lengd gjörgæslulegu, skráning á víkkun sjáaldurs, blóðþrýstingsfall og fall í súrefnismettun og blóðleysi með hemoglóbín gildi < 80 g/dL. Hunt og Hess skor var skráð fyrir ISB hóp og Injury Severity skor fyrir HÁ hóp. S100b var mælt í öllum sjkl. við innlögn. Í rannsókninni tóku þátt 21 HÁ sjkl., 6 með miðlungs alvarlegan HÁ og 15 með alvarlegan HÁ, og 19 ISB sjkl..

Niðurstöður: Sykursteraöxullinn: HÁ hópurinn hafði marktækt lægra kortisól en ISB hópurinn við innlögn, undir viðmiðunargildum voru 23,8% borið saman við 0% í ISB hópnum. Dag 6 var einn sjkl. í hvorum hóp sem hafði kortisól undir viðmiðunargildi, 6,7% af HÁ hópnum og 9,1% af ISB hópnum. Kynhormónaöxullinn: Í karlmönnum á degi 0 var truflun hjá 52,9% í HÁ hópnum og 57,1% í ISB hópnum. Á degi 6, 84,6% í HÁ hópnum og 90% í ISB hópnum. Það var meiri bæling á LH/FSH í HÁ hópnum. Skjaldkirtlishormónaöxullinn: Einn TBI sjkl. (5,9%) hafði miðlægan skjaldvakabrest á degi 6. Vaxtarhormónaöxullinn: Á degi 0 höfðu 52.4% í HÁ hópnum og 35.7% í ISB hópnum lágt IGF. Á degi 6 höfðu allir nema einn HÁ sjkl. (5.9%) eðl IGF-1 gildi en 25% í ISB hópnum enn lág IGF-1 gildi.

Þegar tengsl hormónatruflana og alvarleika áfalls voru skoðuð var almennt með auknum alvarleika aukin truflun/bæling á kynhormóna- og skjaldkirtilshormónaöxlinum og aukin virkjun á sykursteraöxlinum.

Ályktanir: Hormónatruflanir í bráðafasa HÁ og ISB eru algengar. HÁ sjkl. eru í hættu á að fá sykursteraskort en að greina slíkan skort réttilega er erfitt en um leið mjög mikilvægt. Algengasta truflun á heiladingulsöxli var í kynhormónaöxli. Aukin bæling á kynhormóna- og sykursteraöxlinum á heiladingulstigi öxulsins sem og munur á bælingu vaxtarhormónaöxulsins milli HÁ og ISB sjkl. getur bent til að það sé munur á meingerð hormónatruflana hjá HÁ og ISB sjkl. Hvort hormónabreytingar í bráðafasa HÁ og ISB sé eðlileg aðlögun eða ekki er óljóst sem og klíniskt mikilvægi þessara truflana annarra en í sykursteraöxlinum. Frekari rannsókna er því þörf. Meðhöndlandi læknar ættu að meta sykursteraöxulinn þegar ábending er til staðar. Skimun fyrir öðrum hormónatruflunum gæti bent til þarfar á eftirfylgd í síðfasa HÁ og ISB.

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.

Methods: The study was a prospective single-center study. Anterior hypothalamic-pituitary (HP) hormone axis were assessed on admission (day0) 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.

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 and on day 6, 84.6% of TBI patients and 90% of SAH patients had suppressed HP-gonadal axis. 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 disturbance in the acute phase of TBI and SAH is common. TBI patients are at risk for corticosteroid insufficiency (CI) but the diagnosis of CI is difficult but the at the same time very important to diagnose. The HP-gonadal axis was the most commonly disturbed axis. Greater suppression of the HP-gonadal and adrenal axis at the pituitary level in TBI patients as well as difference in somatotroph disturbance may be explained by different causative mechanisms for hormonal disturbance in TBI and SAH patients. The clinical significance of these disturbances, other than the HP-adrenal axis, whether adaptive or maladaptive is uncertain. Further studies are needed on the subject. Clinicians should evaluate the HP-axis on indication as treament with hydrocortisone can be lifesaving. 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.

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Table of contents

List of figures

List of tables

List of abbreviations

ACTH	Adrenocorticotropic hormone
ADH	Antidiuretic hormone
APACHEII	Acute Physiology and Chronic Health Evaluation II
ATLS	Acute trauma life support
BBB	Blood brain barrier
CRCI	Critical illness related corticosteroid insufficiency
CI	Corticosteroid insufficiency
E2	17 b-estradiol
eNOS	Endothelial nitric oxide synthase
FSH	Follicle stimulating hormone
fT4	Free thyroxine
GH	Growth hormone
GCS	Glasgow coma scale
HP	Hypothalamic-pituitary
ICP	Intracranial pressure
ICU	Intensive care unit
IGF-1	Insulin like growth factor1
IH	Inhibiting hormone
iNOS	Inducible nitric oxide synthase
LH	Luteinizing hormone
LUH	Landspitali – National University Hospital of Iceland
mTBI	Moderate traumatic brain injury
p-ACTH	Plasma levels of adrenocorticotropic hormone
PRL	Prolactin
QoL	Quality of life
RH	Releasing hormone
SAH	Subarachnoid hemorrhage

Sjkl.	Sjúklingur
sTBI	Severe traumatic brain injury
T3	Triiodothyronine
T4	thyroxin
TBI	Traumatic brain injury
TSH	Thyroid stimulating hormone
WFNS	World Federation of Neurosurgeons Classification

1 Introduction:

1.1 Traumatic brain injury:

Traumatic brain injury (TBI) is a leading cause for permanent disability and death among young people. The reported incidence of hospitalized and fatal TBI in Europe is 235 per 100,000/year and the mortality rate 15.4 per 100,000/year. Furthermore, of the yearly incidence mild TBI (see TBI classification below) is 79%, moderate 12% and severe 9% (1). The annual incidence for hospitalized head injury in Iceland decreased from 181 per 100.000/year in the year 2000 to 110 per 100.000/year in the year 2009 (2). Even higher incidence has been reported in the USA or 538/100.000 (3).

The prevalence of neurological and functional impairments after moderate and severe TBI (see classification below) has been reported to be 1-2% meaning that in the USA 3,2-5,3 million people are living with sequel from moderate and severe TBI (4).

During the years 1990-2000, the average mortality from TBI in Iceland with roughly 300.000 inhabitants was 32/year (5).

1.1.1 Classification of TBI severity:

TBI has traditionally been classified into mild TBI, moderate TBI (mTBI) and severe TBI (sTBI) by an injury severity score the Glasgow Coma Scale (GCS). Points are given for eye-opening (1-4), verbal response (1-5) and motor response (1-6). Severity is defined as: mild injury score of >13, moderate 9 to 13 and severe injury ≤8 as shown in table 1 (6). There are numerous other scoring systems that grade consciousness and disability after TBI but GCS is the most commonly used. TBI can even be classified by mechanism of injury, direct or indirect, blunt or penetrating trauma and on radiologic findings as the Marshall CT classification (7).

Table 1. The Glasgow Coma Scale

	1	**2**	**3**	**4**	**5**	**6**
Eye response	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal response	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	N/A
Motor response	Makes no movements	Extension to painful stimuli (decerebrate response)	Abn flexion to painful stimuli (decorticate response)	Flexion/ Withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

Points are given for eye-opening, verbal and motor response and the sum is the GCS score. N/A not applicable, Abn = abnormal.

1.1.2 Pathophysiology of TBI:

TBI occurs when a traumatic event injures the brain. It is a heterogeneous disorder but can be divided into primary and secondary brain injury. Primary brain injury occurs at the time of the trauma caused by external mechanical forces resulting in contusions, hematomas and white matter shearing and

swelling. Primary injury can be either an impact, a direct contact with an object causing trauma, or a non-impact such as rapid acceleration and deceleration (8).

Secondary brain injury is the result of TBI causing early ionic and neurotransmitter disorder that initiate a cascade of events that disrupt normal cellular function, including changes in glucose metabolism, free radical production, mitochondrial dysfunction, inflammatory response and secondary ischemia. Secondary injury can continue for days causing death of neurons, cerebral edema and increased intracranial pressure (ICP) that can further exacerbate the brain injury. Its symptomatic presentation varies with each individual, injury type, injury severity, age and gender, making it challenging to diagnose, understand and treat. Research efforts to understand the common underlying neurochemical and metabolic responses to TBI could provide further therapeutic options for early intervention of TBI in patients of all ages (8,9).

1.1.3 Predicting prognosis after TBI:

Regarding prognostic factors and TBI, the endpoint is often neurological outcome after 6 months or death. A good prognostic model can aid in resource allocation, estimation for need of further follow up, researches and treatment, communication with patients´ family and study designs. Prognostic models using baseline characteristics can predict death and 6 month outcome (10,11). An example is the model presented by the MRC CRASH trial collaborators predicting 14 day mortality and 6 month outcome as depicted in figure 1 (12).

1.1.4 Biomarkers in TBI, S100b:

There is a large interest in developing biomarkers both as diagnostic tools as well as prognostic markers in brain injury. Brain biomarkers usually are proteins that can be repeatedly and safely measured from biofluids. Among these is S100b which has been extensively studied. S100b is a small, dimeric calcium-binding protein, located in the cytoplasm and nucleus of a wide range of cells and involved in the regulation of a number of cellular processes, such as cell cycle progression and differentiation. Among cells expressing S100b, glial and neural cells of the CNS are the most abundant, thus it can be detected in serum following TBI (13). Raabe et al showed a significant correlation between volume of contusion visible on CT scan and serum S100b concentration (14). In a systematic review by Mercier et al on S100b and mTBI and sTBI there was a significant association between serum concentrations of S-100b protein and unfavorable prognosis as defined by mortality, Glasgow outcome score = 3, and brain stem death (15).

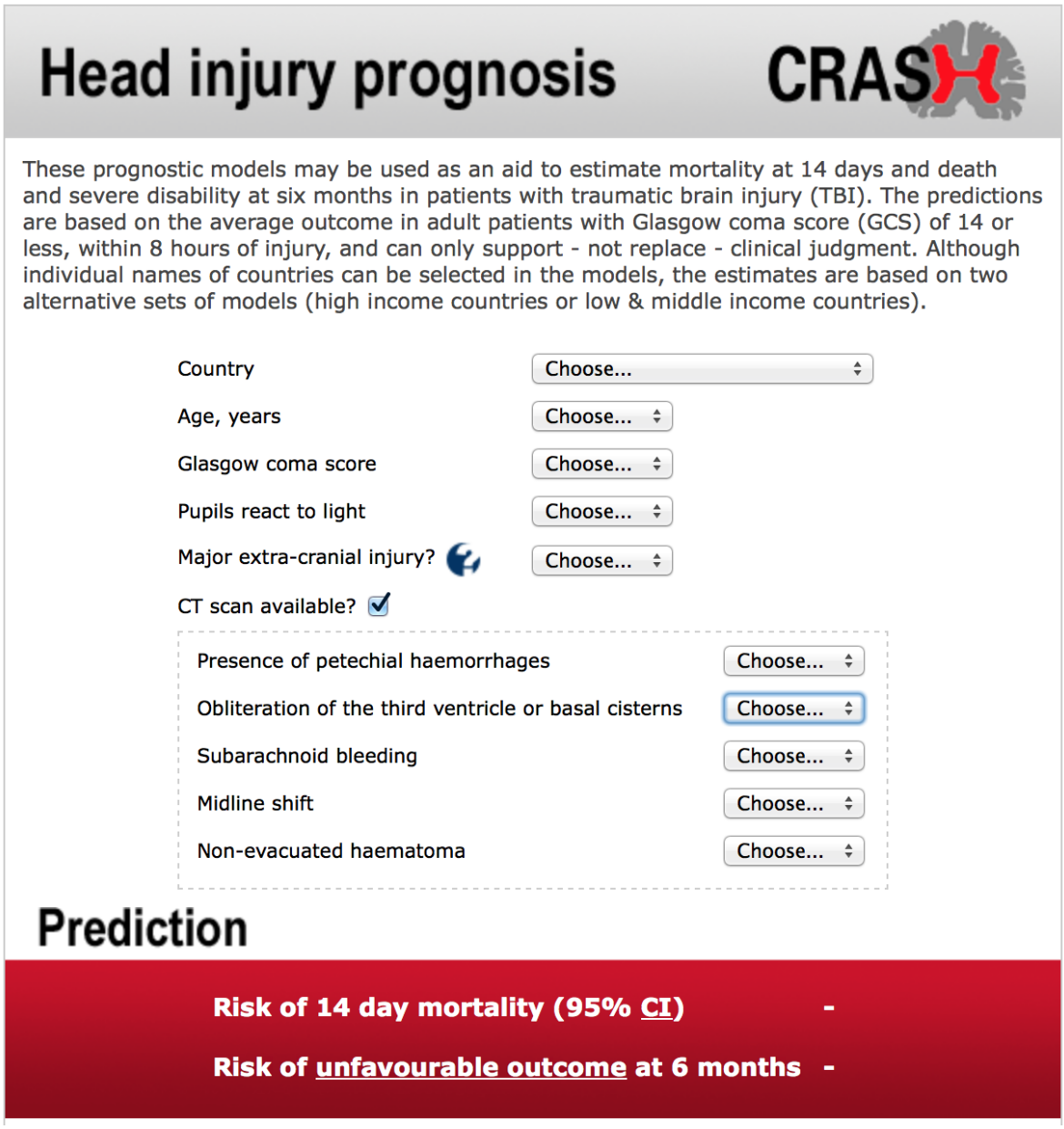

Figure 1. The Crash prognostic model (Source: http://www.trialscoordinatingcentre.lshtm.ac.uk)

1.1.5 Treatment of TBI:

Describing the treatment of TBI in details is out of the perspective of this thesis. For simplification it could be said that the treatment of TBI aims at minimizing secondary injury as the primary injury is often irreversible. It follows the concept of acute trauma life support (ATLS). It starts in the prehospital settings and continues in the emergency department and the intensive care unit (ICU). It aims at correcting the physiologic disorder previously described as well as treating other injuries and complications.

Physiologic disturbance following the initial insult, causing brain injury, can exacerbate secondary brain injury. These may include hypotension, hypoxia, hyper- and hypocapnia, hypo- and hyperthermia, metabolic acidosis, seizures, coagulopathy, hyperglycemia, and raised ICP. Hypoxia

and hypotension combined may result in an increased mortality rate by 70%. It has been proposed that the treatment of the patient with TBI should aim at preventing and correcting these physiologic derangements (16–20) It has also been suggested that intracranial hypertension, ICP>20mmHg, recorded initially or during neurological deterioration is a strong predictor of negative outcome (21).

Apart from supporting therapy, surgery is a well-established treatment. Mass lesions such as hematomas or contusions that may cause increased ICP or shifting of intracranial structures can be surgically removed. Refractory elevated ICP can even be treated with decompressive craniotomy where part of the skull is removed. Indications for surgical therapy and timing of surgery are based upon neurologic status and CT findings and the nature of the TBI and type of bleeding (22–26).

1.1.6 Neuroprotective treatment of TBI:

There is great interest in neuroprotective pharmacologic treatment aimed to ameliorate the secondary injury cascade of events that disrupt normal cellular function and lead to cell death. There have been numerous candidates as seen in table 2 and research is ongoing but no agent has reached its way to clinical practice (9). Of these corticosteroids, progesterone, estrogen and insulin like growth factor 1 (IGF-1) are of special interest in this thesis.

Table 2. Overview of candidates as neuroprotective agents

Agents that have been tested in clinical trials or are being tested in ongoing clinical trials.	Anatibant, Ciclosporin, Deltibant, Pegorgotein, Progesterone, Traxoprodil, Dexanabinol, Magesium sulphate, Nimodipine, Rosuvastatin, Selfotel, Tirilazad, Amantadine, Citicoline, Darbepoetin-α, Estrogen, Glibenclamide, human choriconic gonadotropin, recombinant erythopoietin, Minocycline, N-acetyl-cysteine, Oxycyte perfluorcarbon emulsion, Propranol, Clonidin,
Experimental agents with positive in vivo or in vitro evidence	Nicotinamide, Ethyl pyruvate, N-acetyl cysteine, S-nitrosglutathione, Bortezomib, Glyceryltriacetate, Ketogenic diet, BIBN 99 (muscarinic antagonist), Lazaroid U-83836E, NNZ-2566 (glycine-proline-glutamate analogue, Ziconitide, mGlu antagonists, Stilbazulenyl nitrone, Insulin-like growth factor-1, Basic fibroblast growth factor, Nimesulide, Enoxaparin, Minocycline, Rifuzole, Erythropoetin, Pyridoxine, Bromocriptine, S100B, BAY 28-7271 (cannabinoid agonist) Nitric oxide synthase inhibitors, Edavoarone (NMDA-antagonist) AMPA antagonists.

Reproduced from McConeghy et al (27)

Corticosteroids attenuate vasogenic edema and swelling. A systematic review in 1997 suggested an absolute risk reduction of 1-2% in corticosteroid treated TBI patients. The systematic review consisted of trials which altogether included about 2000 patients. One of the conclusions were that a large randomized controlled trial was needed (28). In the CRASH trial TBI patients were randomized to either receive high dose methylprednisolone or placebo. The trial revealed that routinely giving corticosteroids to TBI patients resulted in an increase in relative risk, compared to conventional treatment, of death. With a relative risk of 1.18, 2 weeks after trauma, and 1,15, 6 months after trauma (29,30). The CRASH trial included patients with mild TBI, mTBI and sTBI and supraphysilogic doses of

methylprednisolone were given as a routine. The question remains whether there is a subgroup of TBI patients that might benefit from treatment with corticosteroids as neuroprotective treatment.

Progesterone´s neuroprotective effect is not completely understood but clearly is multimodal. It limits cerebral edema and shows anti-inflammatory and anti-apoptotic and some anti-oxidant properties which enable it to protect against the breakdown of cell membranes that leads to the death of neurons and glia (31). A systematic review by Ma et al included three randomized controlled studies, with a total of 315 sTBI patients, and reported a relative risk of death or severe disability in patients treated with progesterone to be 0.77, compared to no treatment with progesterone. Further studies are needed on progesterone and TBI (32).

Estradiol has showed neuroprotective potency in various animal models. It affects modulation of synaptic transmission, regulation of apoptosis, control of oxidative stress and inflammation (9,33).

IGF-1 has neurotropic effects, influences synaptic plasticity, neurotransmitters, metabolic and energy dynamics and vascular reactivity. TBI rat model have demonstrated that IGF-1 improves cognitive and motor outcomes. Clinical exposure to this investigational agent is limited in TBI and studies in human TBI were affected by pharmacokinetic disposition of IGF-1. Recent advances in drug formulations for IGF-1 may provide opportunity for renewed clinical trials of this agent in patients with TBI (9).

1.2 Subarachnoid hemorrhage:

SAH accounts for 5% of all strokes. It is a medical emergency and has a mortality of nearly 50% (34). Survivors often suffer from neurocognitive squeal such as fatigue, mood disturbances, anxiety and depression and 46% of survivors have cognitive impairment (35). Less than 20% of survivors have no residual symptoms (36).

1.2.1 Classification of SAH:

As for TBI the GCS is used for assessing level of consciousness. There are three specialized scoring systems for evaluating SAH, two clinical scoring systems Hunt and Hess and the World Federation of Neurosurgeons Classification (WFNS) who are explained in tables 2 and 3. The Fisher CT score is based on radiologic findings (37). For each of these scoring systems a higher number predicts a worse outcome (38).

Table 3 The Hunt and Hess scale

Grade	Signs and symptoms
1	Asymptomatic or minimal headache and slight neck stiffness
2	Moderate to severe headache, neck stiffness, no neurologic deficit
3	Drowsy, minimal neurologic deficit
4	Stuporous, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances
5	Deep coma, decerebrate rigidity, moribund

Table 4. The World Federation of Neurosurgeons Classification

Grade	GCS	Focal neurological deficit
1	15	Absent
2	13-14	Absent
3	13-14	Present
4	7-12	Present or absent
5	<7	Present or absent

GCS = Glasgow Coma Scale

Table 5. The Fisher CT grading score

Grade	Appearance of blood on head CT scan
1	No blood detected
2	Diffuse deposition or thin layer of blood, < 1mm thick
3	Localized clots or blood layer >1 mm thick
4	Intracerebral or intraventricular clots with diffuse or no subarachnoid blood

1.2.2 Epidemiology and risk factors for SAH:

In a systematic review by de Rooji et al the total incidence of SAH was 9/100.000/year but there was a substantial geographical variance with the lowest reported rates in in South and Central America, 4.2/100.000/year, and the highest rates in Japan, 22.7/100.000/year, and Finland 19.7/100.000/year.

Incidence for SAH increases with age and women had a relative risk of 1.24 times compared to men (39). There is one Icelandic study with a reported incidence of 8/100.000/year (40).

Hypertension, cigarette smoking and family history are among the most consistently observed risk factors for SAH (41).

1.2.3 Pathophysiology of SAH:

Saccular aneurysm cause 80-85% of SAH but other causes include trauma, arteriovenous malformations, intracranial arterial dissections, bleeding diatheses and illicit drugs especially cocaine and amphetamine.

With a rupture of an aneurysm there is a direct bleeding into the cerebrospinal fluid under arterial pressure causing the blood to spread rapidly in the CSF and raising ICP. The bleeding can invade the brain parenchyma. The bleeding usually lasts only a few seconds but re-bleeding is common.

The primary bleeding can result in secondary events which further contribute to brain injury. Hydrocephalus caused by obstruction of CSF flow by blood or adhesions or decreased CSF absorption at arachnoid granulations (42). Vasospasm, caused by spasmogenic substances from the lysis of subarachnoid blood clots, can cause regional hypoperfusion and ischemia (43). Raised ICP is caused by the hemorrhage, hydrocephalus, hyperemia and distal cerebral arteriolar vasodilation (44).

1.2.4 Treatment of SAH:

Describing the treatment of SAH in details is out the scope of this thesis. Treatment aims at preventing re-bleeding by surgically clipping the aneurysm or with coiling with endovascular technique. Furthermore treatment aims at minimizing and treating secondary events such as vasospasm, raised ICP and hydrocephalus and treating complications and supportive treatment in the ICU (34).

1.2.5 Neuroprotective treatment:

17 b-estradiol (E2) and progesterone are potential therapeutic agents in SAH although clinical evidence is lacking. E2 has been shown in animal models to attenuate vasospasm after SAH, promote neuronal survival, inhibit neuronal apoptosis and decrease oxidative damage and inflammation. These protective effects are mediated partly through E2 effects on endothelial nitric oxide by activating endothelial nitric oxide synthase (eNOS), preventing increased inducible NOS (iNOS) and decreasing endothelin-1 production (45,46).

Progesterone may reduce brain injury after SAH by inhibiting cell apoptosis and stabilizing the blood brain barrier (BBB). Progesterone attenuates vasospasm after SAH by affecting endothelial nitric oxide (47,48).

1.3 The piuitary gland:

The pituitary gland, or hypophysis, is an endocrine gland. Weighing only 600 mg. It lies in a bony cavity called the sella turcica as shown in figure 2. It is a protrusion from the bottom of the hypothalamus and is covered by dura. The pituitary is divided in three lobes, anterior (or adenohypophysis), intermediate often considered part of the anterior pituitary and the posterior

pituitary (or neurohypophysis). Hormone release from the pituitary is controlled by the hypothalamus, table 4 provides an overview of the different hypothalamic-pituitary (HP) hormone axis (49).

The blood supply to the pituitary is illustrated in figure 3. The long hypophyseal portal vessels that lie in the infundibulum provide the anterior pituitary gland with 70-90% of its blood supply. They arise from branches of the internal carotid artery and anterior Circle of Willis. The short hypophyseal portal vessels that arise from the branches of the intracavernous internal carotid artery supply the anterior pituitary gland with less than 30% of it blood supply, mostly the medial portion of the gland (50)

The posterior pituitary (or neurohypophysis) develops as an extension of the hypothalamus. Cell bodies in the hypothalamus project axons down the pituitary stalk (or infundibulum) where they secrete antidiuretic hormone (ADH) and oxytoxin.

The anterior pituitary (or adenohypophysis) is distinct from the posterior pituitary and does not have the neuronal composition. Hypothalamic hormones are secreted to the anterior lobe through the hypothalamic-hypohysial portal system. The anterior pituitary secretes cortico-, thyro-, gonado-, somato- og lactotrophins and thus regulates several physiological processes. The intermediate lobe secretes melanocyte stimulating hormone (49).

Table 6. Hypothalamic, pituitary hormones and target organs/cells.

Axis	**Hypothalamic hormone**	**Anterior pituitary hormone**	**Target cells/organs**	**Main effect**
Corticotrophic (HP-adrenal)	Corticotropin RH (CRH)	Adrenocorticotropic hormone (ACTH)	Adrenal cortex	Stimulates adrenal cortex secretion of corticosteroids,
Gonadotrophic (HP-gonadal)	Gonadotropin RH (GnRH)	Luteneizing hormone (LH) and Follicle stimulating hormone (FSH)	Ovaries and testes	FSH regulates oogenesis and spermatogenesis and LH causes ovulation and release of testosterone
Thyrotrophic (HP-thyroid)	Thyrotropin RH (TRH)	Thyroid stimulating hormone	Thyroid gland	Stimulates secretion of thyroid hormones
Somatotrophic (HP-somatotrophic)	Growth hormone RH (GHRH) Growth hormone IH (somatostatin)	Growth hormone (somatotropin)	Bone, muscles, liver, adipose tissue and cells in general	Stimulation of growth and metabolism of carbohydrates and lipids, stimulates liver to produce IGF-1

Hypothalamic hormone either stimulates anterior pituitary with releasing hormone (RH) or inhibits the anterior pituitary witt inhibiting hormone (IH). HP = Hypothalamic pituitary.

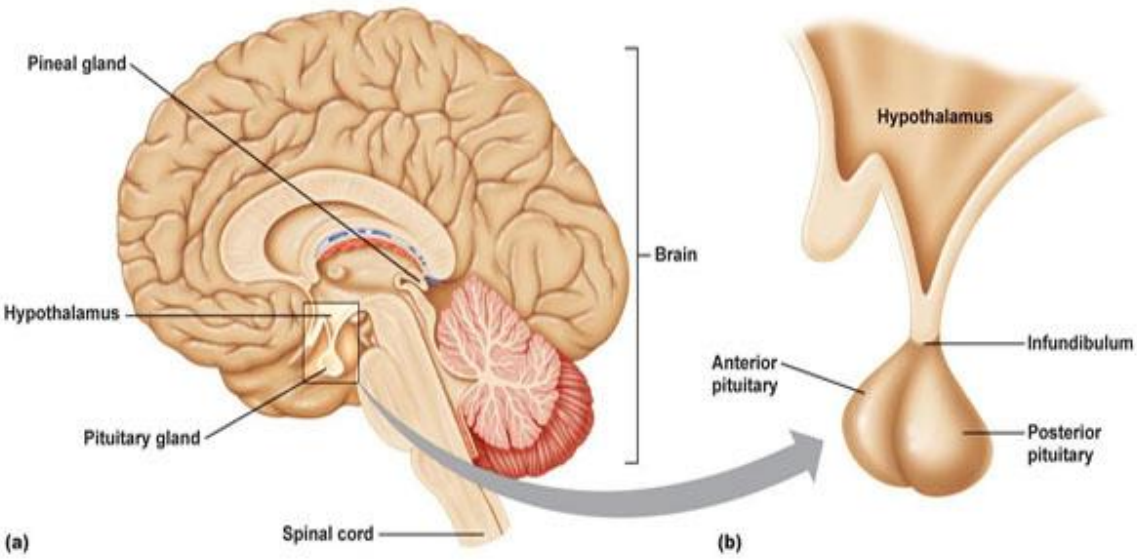

Figure 2. The pituitary gland and its anatomy (Source Organsofthebody, http://www.organsofthebody.com/pituitary-gland/)

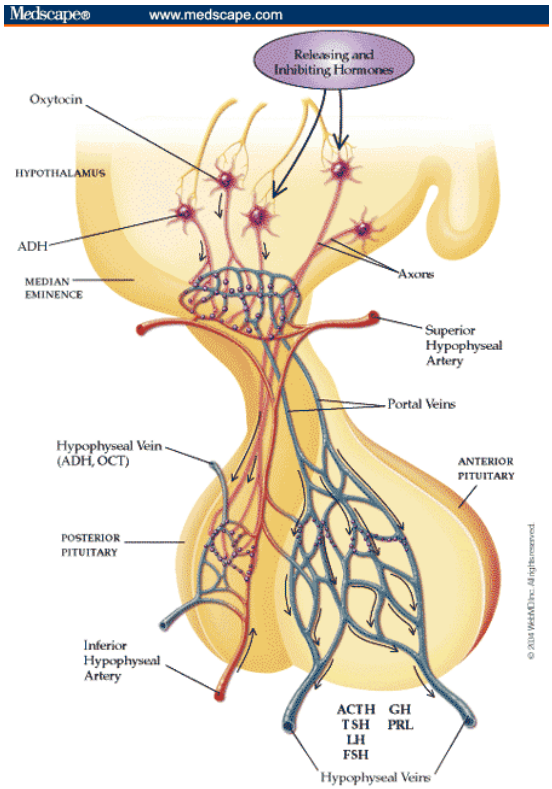

Figure 3 The pituitary gland, anatomy, vasculature and connection to the hypothalamus (Source: Medscape, http://www.medscape.com/viewarticle/518323_3)

1.4 The endocrine response in critical illness:

Critical illness puts the patient to the ultimate severe physical stress. The immediate stress response includes among other endocrine adaptation, presumably for providing the required energy for acute survival postponing anabolism. Alterations within the different hypothalamic-pituitary axes cause lipolysis, proteolysis and gluconeogenesis. This same response can then become maladaptive and hamper recovery when the immediate threat is over and the patient suffers from prolonged critical illness (51,52).

1.4.1 Diagnosing endocrine dysfunction in the critically ill patient:

Critically ill patients experience great physiological stress with effects on the inflammatory pathways, tissue perfusion and resulting multi-organ dysfunction. These changes as well as treatment in the ICU result in a dynamic endocrine response. Appropriate basal levels of hormones are different in the critically ill due to changes in secretion, loss of negative feedback, altered target tissue receptor function and impaired enzymatic clearance. Thus the critically ill patient differs fundamentally from the usual endocrine outpatient and the evaluation of their endocrine systems. Commonly used endocrine tests should be used with caution and dynamic tests are often unsuitable due to slow turnaround or issues with safety (51).

1.4.2 Hypothalamic-pituitary adrenal axis in critical illness:

Cortisol plays a pivotal role in the stress response. Both high and low levels have been associated with mortality (53). Cortisol shifts carbohydrate, fat and protein metabolism and delays anabolism and thus likely contributes to the provision of extra energy to vital organs. Furthermore cortisol affects the hemodynamic system by intravascular fluid retention and enhancing inotropic and vasopressor responses to catecholamines and angiotensin II (52).

During critical illness there is a high cortisol level but plasma ACTH levels tend to be low. Cortisol synthesis can be affected by critical illness per se via cytokines as well as treatment for example the anesthetic agent etomidate and the fungicide ketoconazole (54,55). Cytokines furthermore cause increased corticosteroid metabolism, decreased corticosteroid receptor and tissue resistance to corticosteroids. Changes in free cortisol levels may be caused by changes in plasma concentration of cortisol binding globulin, albumin and hepatic cortisol metabolism (56). Newer evidence suggests even that high levels of cortisol during critical illness is caused by reduced cortisol plasma clearance rather than increased production. That cortisol production is only moderately increased and only in patients suffering from systemic inflammatory response syndrome (57).

Diagnosing corticosteroid insufficiency in critical illness has been the subject of much debate. In a consensus statement from an international task force by the American College of Critical Care Medicine critical illness-related corticosteroid insufficiency (CRCI) is said to be caused by adrenal insufficiency together with tissue corticosteroid resistance and is characterized by an exaggerated and protracted proinflammatory response. It should be suspected in hemodynamically instable patients refractory to treatment. The diagnosis is best made by a random cortisol of < 276 nmol/L or an increase <248 nmol/L with a Synacthen test (58).

1.4.3 Hypothalamic-pituitary thyroid axis in critical illness:

Critical illness affects the HP-thyroid axis by changes in metabolism. Thyroid hormone metabolism as well as medication commonly used in the ICU settings affect thyroid hormone balance. As much as 70% of critically ill patients may have what is called the non-thyroidal illness syndrome or low T3 syndrome or euthyroid sick syndrome. The syndrome is characterized by low serum levels of triiodothyronine (T3) and high levels of reverse T3, with normal or low levels of thyroxin (T4), free T4 (fT4) often in the normal range and normal or low levels of thyroid-stimulating hormone (TSH). These changes probably result from changes in peripheral metabolism of thyroid hormones, TSH regulation and binding of thyroid hormone to transport-protein and receptor binding and intracellular uptake (59). Low T3 levels are partially related to fasting and that part of the response seems adaptive and treatment is likely not indicated (52).

1.4.4 Hypothalamic-pituitary gonadal and lactotroph axis in critical illness:

Testosterone is the most important endogenous anabolic steroid and changes in the gonadal axis could be important with regard to the catabolic state of critical illness in men. Testosterone levels immediately decrease after acute insult e.g. surgery or myocardial infarction. Acute critical illness is associated with mildly low testosterone levels, which become more severely reduced with chronic critical illness. This may be because of direct inhibition on Leydig cells or effects of cytokines. A plausible explanation, at least in the acute phase for decreased secretion of anabolic androgens, is that the body is reducing energy consumption and conserving substrates for more vital functions and thus it is an adaptive response. In the chronically critically ill patient this might though be maladaptive (60,61).

Prolactin has a wide range of effect, stimulating lactation, suppressing gonadotropins and presumed to have immune-enhancing properties. It is a known stress hormone. In the chronically ill critical patient prolactin levels are lower than in the acute phase (61).

1.4.5 Hypothalamic-pituitary-somatotroph axis in critical illness:

Growth hormone (GH) has mitogenic and anabolic action via increased production of IGF-1 resulting in nitrogen retention, protein anabolism and linear growth. GH does have in itself metabolic action, causing lipolysis, enhanced amino acid transport into muscle and anti-insulin effects but those of IGF-1 are more prominent. Initially with acute stress the mean concentration of GH is acutely increased due to increase in interpulse GH levels but IGF-1 levels on the contrary are low indicating a GH resistance. In prolonged critical illness the GH levels are only slightly elevated but there are decreased pulsatile tops of GH concentration (62,63)

1.4.6 Therapeutic implications:

As described above there is a dynamic hormonal response during critical illness. Some probably physiologically adaptive while other may be maladaptive. Manipulation may be in the form of replacement with physiological doses of hormones or pharmacological with supraphysiological doses.

Further research is needed to establish the benefits and possible harm caused by endocrine manipulation in critical illness (51)**.**

1.5 Neuroendocrine disturbances following TBI and SAH:

Pituitary dysfunction following TBI was first reported in 1918 by Cyran in a patient with skull base fracture (64). Hoff reported in 1961 three cases of hypopituitarism associated with intracranial aneurysm (65). TBI and SAH can cause neuroendocrine changes both in the acute phase as well as in the chronic phase of survivors.

1.5.1 Prevalence of hypopituitarism in the late phase following TBI and SAH:

Several studies on the prevalence of anterior pituitary dysfunction have been published the last decade with Kelly et al being among the first to publish a systematic study on mTBI and sTBI patients and reporting a total prevalence of 36,4% of anterior pituitary dysfunction (66). Later in a systematic review of 19 studies with a total of 1050 subjects Schneider et al published a pooled prevalence of anterior pituitary dysfunction, for all TBI, 27,5% (range 15-68%). The prevalence was highest for sTBI 35,3% and 10,9% and 16,8% for mTBI and mildTBI patients respectively. In the same systematic review the prevalence of anterior pituitary dysfunction in SAH patients was 47% (range 37.5-55.9%) based on 5 studies with a total of 122 patients (67).

1.5.2 Natural course of hypopituitarism following TBI and SAH:

Neuroendocrine changes in the acute phase have not been shown to predict hypopituitarism in the chronic phase with endocrine abnormalities in the acute phase often resolving in some patients while others developing hypopituitarism at later stages (68–70). Hypopituitarism has even been shown to either resolve or develop between early chronic phase at 3 months and 6-12 months (71,72). Studies show similar results for hypopituitarism following SAH where some patients experience a transient anterior pituitary dysfunction resolving over time and other developing hormonal deficiencies with time (73–75). Prevalence of long-term hypopituitarism following SAH varies though with Klose et al finding no evidence of hypopituitarism following SAH in a cohort of 62 patients (76) while others have reported a prevalence of 38-45% (73,77–79).

1.5.3 Predictive factors for hypopituitarism following TBI and SAH:

No good predictive factor has been identified for anterior pituitary dysfunction following TBI and SAH making screening difficult.

Some studies show that sTBI with lower GCS increases risk for anterior pituitary dysfunction (66,70,80,81). Other studies have not shown this increased risk with more severe TBI (69,73,82).

Klose et al found the risk to be increased in patients with high ICP, longer hospital stays and longer intubation in a cross sectional study of 104 TBI patients (83). These results were not confirmed in a prospective study by Klose et al (70). Ischemic insults that is hypotension or hypoxia have been identified as predictive factors (66).

CT findings have been also studied as risk factors indicating that more severe injury is a risk factor for developing anterior pituitary dysfunction (66,72) as well as basilar skull fracture (84,85).

Although no good predictive factor has been identified for anterior pituitary dysfunction following TBI there is a very low probability of diagnosing hypopituitarism in patients with mild TBI, normal CT, or normal intracranial pressure because of the negative predictive value of these factors (86).

Like for anterior pituitary dysfunction following SAH there is no good predictive factor known. Severity judged clinically by Hunt and Hess or radiologic severity by Fisher CT score has not been shown to be of value as predictive factor (73,77–79). One study has shown the occurrence of cerebral vasospasm and hydrocephalus in the acute phase of SAH to be a risk factor (87).

1.5.4 Neuroendocrine disturbances in the acute phase of TBI and SAH:

Several studies have assessed the neuroendocrine changes in the acute phase of TBI. Studies are available although fewer on the same subject in the acute phase of SAH. The design, methodologies and main results of these studies are summarized in tables 7 and 8.

As demonstrated in tables 7 and 8 previous studies show different results on the nature of neuroendocrine changes in the acute phase of TBI and SAH. Also demonstrated is that previous studies differ in patients selection, methodology and timing of assessment which can explain varying results.

Table 7. Summary of studies evaluating neuroendocrine changes in the acute phase of TBI.

				Neuroendocrine axis assessed % deficient unless stated otherwise					
Study	**Type of patients**	**N**	**Time of testing**	*ACTH*	*GH*	*Gonadal*	*Thyroid*	*PRL*	**Tests and definition of deficiency**
1) Cernak et al. 1999 (88)	mildTBI, sTBI (direct injury), TBI (blast trauma)	31	D0-D7	N/A	N/A	see comment	see comment	see comment	Baseline hormone levels.
2) Agha et al. 2004 (89)	sTBI and mTBI	50	Median D12, (7-20)	16%	18%	79% (male) 90% (pre-menopausal female) 50% (post-menopausal female)	2%	14%	Baseline hormone levels, glucagon stimulatation test for somatotrophic and corticotrophic axis
3) Dimopoulou et al. 2004 (90)	sTBI and mTBI	34	Median D18, (8-55)	24%	24% * see comment	24%	15%	59%	Baseline hormone levels and stimulation test hCRH and GHRH for corticotrophin and somatotrophin. ACTH/cortisol deficiency if response <552 nmol/L. Complete GHdef if peak GH<3mcg/L, partial if 3-5mcg/L
4) Cohan et al. 2005 (91)	sTBI and mTBI	80	D0 - D9	53%	N/A	N/A	N/A	N/A	Baseline hormone levels. ACTH/cortisol deficiency defined as two consecutive measurements of cortisol <414 nmol/L or one measurement of cortisol <138 nmol/L
5) Tanriverdi et al 2006 (69)	sTBI, mTBI and mildTBI	52	D0	9,8%	20,4%	41,6%	↓ Low T3 sx 51,9% ↓ TSH 5,8%	↑PRL 12%	ACTH/cortisol deficiency defined as cortisol <193 nmol/L , GH deficiency if IGF-1 <84ng/mL
6) Klose et al. 2007 (70)	sTBI, mTBI and mildTBI	46	D0 – D12 median time not noted	4%	N/A	67%	33%	39%	Baseline hormone levels, Synacthen test, ACTH/cortisol deficiency defined as peak or 30 min cortisol < 500 nmol/l

Continuing table 7.

				Neuroendocrine axis asessed % deficient unless stated otherwise					
Study	**Type of patients**	**N**	**Time of testing**	*ACTH*	*GH*	*Gonadal*	*Thyroid*	*PRL*	**Tests and definition of deficiency**
7) Kleindienst et al. 2009 (92)	sTBI, mTBI and mildTBI	57	D0, D3, 7	D0: 22% D3: 25% D7: 18%	D0: 41% D3: 40% D7: 27%	D0: 13% D3: 24% D7: 18%	D0: 17% D3: 24% D7: 8%	D0: 15% D3: 9% D7: 13%	Baseline hormone levels. ACTH/cortisol deficiency defined as baseline cortisol < 290nmol/L
8) Tandon et al 2009 (93)	sTBI	59	D0, D15	D0: ↑Cortisol 53% D15: ↑Cortisol 43%	Only measured GH D0: ↑GH 17% D15: ↑GH 26%	Only measured LH and FSH D0: ↑LH 17%, ↑FSH 8,5% D15: ↑LH 7,4% ↑FSH 13%	D0: ↓ T3 1,7% ↑ T4 5,1% ↓ TSH 1,7% ↑ TSH 15,3% D15: ↓ T4 1,9% ↑ T4 3,7% ↑ TSH 14,8%	D0: ↑PRL 30,1% D15: ↑PRL 37%	Baseline hormone levels. ACTH/cortisol deficiency defined as cortisol below reference range 138 -690 nmol/L
9) Chourdakis et al. 2011 (94)	sTBI	59	D0, D6, D12	N/A	N/A	N/A	N/A	N/A	Baseline hormone levels, cortisol, thyroid and testosterone
10) Hannon et al. 2013 (95)	sTBI and mTBI	100	D1, D3, D5, D7, D10	78%	N/A	N/A	N/A	N/A	ACTH/cortisol deficiency defined as baseline cortisol <300 nmol/L

Continuing table 7.

				Neuroendocrine axis asessed % deficient unless stated otherwise					
Study	**Type of patients**	**N**	**Time of testing**	*ACTH*	*GH*	*Gonadal*	*Thyroid*	*PRL*	**Tests and definition of deficiency**
11) Olivecrona et al 2013 (96)	sTBI	45	D1, D4	D1 morning: 54,5% D1 evening: 52,3% D4 morning: 70,5% D4 evening: 59,1%	D1: ↓IGF-1 30,2% D4: ↓IGF-1 2,3%, ↑IGF-1 7,0%	Male only D1: ↓Test 82,1% ↓LH 55,2% ↑LH 6,9% ↓FSH 10,3% ↑FSH 6,9% D4: ↓Test100% ↓LH 58,6% ↑ LH 6,9% ↓FSH 10,3% ↑FSH 3,4%	D1: ↓fT4 5,5% ↑fT4 9,1% ↓TSH 4,5% D4: ↓fT4 27,3% ↓TSH 15,9% ↑TSH 9,1%	D1: ↑PRL 48,3% (male) ↑PRL66,7% female D4: ↑PRL 72,4% (male) ↑PRL 86,7% (female) ↓Prl 3,4%	Baseline hormone levels. ACTH/cortisol deficiency defined as cortisol <276 nmol/L

sTBI = severe traumatic brain injury, mTBI = moderate traumatic brain injury, D = day, ACTH = adrenocorticotropic hormone, GH = growth hormone, IGF-1 = insulin like growth factor 1, PRL = prolactin, TSH = thyroid stimulating hormone, fT4 = free thyroxine 4, Low T3 sx = low t3 syndrome (euthyroid sickness), LH = luteneising hormone, FSH = follicule stimulating hormone, N/A = not applicable.

Comments on studies evaluating neuroendocrine changes in the acute phase of TBI presented in table 7:

1. Cernak et al investigated isolated head trauma from war, mild TBI with closed head injury, sTBI with cranial gunshot trauma and TBI from blast injuries. Compared to healthy controls. In the mTBI group TSH was increased untill D3 and then normalized, TSH was decreased in the sTBI and in the blast injury group initially decreased and then increased. T3 was increased in the mildTBI group but decreased in the other two groups. T4 was the same as the control group. In the mTBI group testosterone was decreased untill D2. Testosterone was profoundly decreased in the sTBI group but not in the blast injury group. Cortisol was initially increased in all groups but was the decreased in the sTBI group (88).
2. Agha et al reported a negative correlation between GCS and prolactin and positive correlation between GCS and testosterone (89).
3. Dimopoulou et al reported that GCS on admission was positively correlated with baseline FSH, peak FSH, testosterone and TSH. 9% of the cohort had partially impaired secretion of GH after stimulation, 15% had low IGF-1 but normal stimulation test (90).
4. Cohan et al. 81% of those diagnosed with adrenal insufficiency had received etomidate. Pat with ACTH/cortisol deficiency were younger, had higher ISS, higher frequency of hypotension, hypoxia and anemia. High dose propofol and penthobarbital was associated with lower cortisol levels (91).
5. Tanrivedi et al reported a positive correlation between testosterone and GCS, negative correlation between prolactin and GCS .Testosterone level was significantly lower in sTBI group compared to other groups (69).
6. Klose et al reported that testosterone and LH was lower with increasing TBI severity and cortisol became higher with increasing TBI severity (70).
7. Kleindienst et al measured urinary excretion of free cortisol and cortisone in 13 patients of which 11had elevated levels and the authors conclude that the normal circadian variation of cortisol is replaced by a more continuous secretion under severe stress. sTBI had more often low TSH and reduced fT4 and low gonadotropins. Noteworthy is that mean initial GCS was 12 and improved to 14 (92).
8. Tandon et al studied 59 patients in the acute phase and later included 40 more patients and followed patients to day 90 and 180 post TBI. No patient had low cortisol on follow up (93).
9. Chourdakis et al compared early enteral feeding vs delayed. Levels of TSH, fT3, fT4 and testosterone declined with time. The decrease of hormonal values was less pronounced in the early enteral feeding group. Cortisol rose in the delayed enteral feeding group but a lesser hormonal change was found in the early enteral feeding group (94).

10. Hannon et al showed that low cortisol was most often during D1 and D3. 62% of those with deficiency had recovered at day 10. Patients with hypocortisolemia had longer ICU stay. Patients in the lowest quartile of mean cortisol and those with low cortisol on D10 had higher mortality (95).
11. Olivecrona et al reported that mean serum fT4 levels decreased but TSH increased from day 1 to day 4. Total testosterone day 1 correlated negatively to GOS at 3 months. LH correlated negatively with Glasgow outcome scale at 3 months. There was a positive correlation between levels of LH day 1 and ICPmax and positive correlation between FSH and Marshall CT score, negative correlation between day 4 TSH levels and Marshall CT grade score. There was a negative correlation between prolactin on day 1 and CPPmin and ICPmax (96).

Table 8. Summary of studies evaluating neuroendocrine changes in the acute phase of SAH.

				Neuroendocrine axis assessed % deficient unless stated otherwise					
Study	**Type of patients**	**N**	**Time of testing**	*ACTH*	*GH*	*Gonadal*	*Thyroid*	*PRL*	**Tests and definition of deficiency**
1) Bendel et al. 2008 (97)	SAH Hunt and Hess 1-5	30	D1, D7	D1: 7% D7: 14%	N/A	N/A	N/A	N/A	ACTH/cortisol deficiency defined as cortisol < 350 nmol/L and low serum ACTH
2) Tanriverdi et al 2007 (79)	SAH, Hunt and Hess 1-4	22	D0	22,7%	22,7%	31,8%	22,7% Low T3 sx	22,7%	Baseline hormone levels. Somatotrop deficiency defined as IGF-1<84 ng/mL. ACTH/cortisol deficiency defined as cortisol <193 nmol/L
3) Klose et al 2009 (76)	SAH, Hunt and Hess 1-5	26	median D7, (2-13)	12%	15%	100% male 88% female	35% low T3 sx	31%	Baseline hormone levels. ACTH/cortisol deficiency defined as baseline cortisol <276 nmol/L
4) Bendel et al 2010 (98)	SAH Hunt and Hess 1-5		D1-D7	N/A	↓IGF-1	N/A	N/A	N/A	Baseline hormone levels
5) Parenti et al 2011 (99)	SAH, Hunt and Hess	60	Within 72 hours from admission	7,1%	22,0%	33,3%	1,8%	N/A	Baseline hormone levels. ACTH/cortisol deficiency defined as cortisol < 172 nmol/L with normal/low ACTH. Somatotrop deficiency defined as IGF-1 < 84 ng/mL
6) Poll et al 2010 (100)	SAH Hunt and Hess 1-5	22	D0, D7 and median D17(14-21)	D0: 0% D7: 0% D17: 4,5%	N/A	N/A	N/A	N/A	ACTH/cortisol deficiency defined as baseline cortisol below refence range 171-536 nmol/L
7)Khursheed et al. 2013 (101)	SAH, WFNS grade 1-5	73	D0	N/A	N/A	12%	0%	18%	Baseline hormone levels

Continuing table 8.

				Neuroendocrine axis assessed % deficient unless stated otherwise					
Study	**Type of patients**	**N**	**Time of testing**	*ACTH*	*GH*	*Gonadal*	*Thyroid*	*PRL*	**Tests and definition of deficiency**
8) Lanterna et al 2013 (102)	SAH, Hunt and Hess 1-3	26	D0-D15	42,3%	N/A	N/A	N/A	N/A	ACTH/cortisol deficiency defined as cortisol <276 nmol/L or a raise of <248 nmol/L after Synacthen test
9) Kronvall et al 2014 (103)	SAH, Hunt and Hess 1-4	51	D5-D10	8%	12%	30%	6% low fT4 with normal TSH	16%	Baseline hormone levels. ACTH/cortisol deficiency defined as cortisol <250 nmol

D = day, ACTH = adrenocorticotropic hormone, GH = growth hormone, IGF-1 = insulin like growth factor 1, PRL = prolactin, TSH = thyroid stimulating hormone, fT4 = free thyroxine 4, Low T3 sx = low t3 syndrome (euthyroid sickness), LH = luteneising hormone, FSH = follicle stimulating hormone, N/A = not applicable.

Comments on studies evaluating neuroendocrine changes in the acute phase of SAH presented in table 8:

1. Bendel et al had 16 elective open clip surgery patients as controls in their study. They concluded that SAH causes an HPA axis response similar to that of elective cranial aneurysm surgery. There was good correlation between serum free and total cortisol concentrations thus measurement of serum free cortisol should not be necessary in SAH patients (97).
2. Tanriverdi et al reported a positive correlations between Fisher's CT scale and cortisol levels and negative correlation between Fisher's CT scale and total testosterone levels (79).
3. Klose et al showed that hormonal alterations were associated with a lower GCS score and the development of hydrocephalus (76).
4. Bendel et al measured IGF-1 in the acute phase and did a follow up at three months. Than IGF-1 had normalized. Patients who scored less on quality of life questionnaire (QoL) had lower IGF-1 in the acute phase (98).
5. Noteworthy to the study of Parenti el al is that the median GCS was 14 (13-15) and median Hunt and Hess 2 (1-3) so they investigated patients with less severe SAH. No gonadotrop deficiency was reported in patients with perimesencphalic bleeding pattern which tend to have a more benign course (99).
6. In the study of Poll et al cortisol was measured at 8:00, 12:00, 16:00 and 20:00. Clearly raised morning values and a consistent decline over the day or a flat curve was considered a normal diurnal cycles, other were deemed abnormal. Normal profiles were associated with shorter length of ICU stay, less complications and better outcome on GOS (100).
7. Khursheed et al even did a follow up 9-12 months post SAH. Prolactin levels and testosterone levels had mostly normalised but 2 patients had developed secondary hypothyroidism. The author conclude that hypopituitarism in not an issue after SAH but they failed to evaluate both cortico- and somatroph axis (101).
8. Lanterna el al reported that ACTH/cortisol deficiency was associated with poor outcome on Glascgow Outcome scale after 1 month. All patients diagnosed with ACTH/cortisol deficiency had a normal Synacthen test (102).
9. Kronvall et al reported that the ruptured aneurysm was more commonly in the circle of Willis among patients with pituitary dysfunction. Patients with pituitary dysfunction had worse Glasgow Outcome Scale (103).

1.5.5 Hypothalamic-pituitary adrenal axis in the acute phase of TBI and SAH:

Dysfunction of the HP-adrenal axis can as previously explained be a life-threatening situation with hemodynamic instability and hyponatremia but can respond rapidly to treatment with glucocorticoids and thus early diagnosis is of value (52,91). Serum cortisol has been found to increase immediately after TBI and then gradually decline to normal levels (88,104).

As demonstrated in table 7 the incidence of ACTH/cortisol deficiency varies between 4-78%. This variation can be explained by difference in methodology and definition of ACTH/cortisol deficiency. Relying solely on Synacthen test in the acute phase can underestimate the incidence as the adrenal glands will still respond to ACTH for up to 6 weeks after pituitary failure (105). Studies relying solely on baseline cortisol levels have used different cut-off levels.

Contrasting results have been reported whether ACTH/cortisol deficiency in the acute phase of TBI continues in to the chronic phase. Tanriverdi et al found an incidence of 9,8% in the acute phase (within 24 hours of admission) in a mixed TBI cohort. At 12 months the prevalence of ACTH/cortisol deficiency was 19,2% with only patient being deficient having new deficiency at 12 months (69). Klose et al reported similar results with all patients diagnosed with ACTH/cortisol deficiency in the acute phase recovering but others developing deficiency (70). Agha et al on the contrary showed in a cohort of 50 TBI patients that in the acute phase 8 patients had ACTH/cortisol deficiency, 4 patients had persistent deficiency at 6 months with 5 patients having developed deficiency and all patients with deficiency at 6 months had persistent deficiency at 12 months (68).

As demonstrated in table 8 the incidence of ACTH/cortisol deficiency in the acute phase of SAH varies between 0-42,3% and as stated above there are conflicting results on persistency of deficiency.

1.5.6 Hypothalamic-pituitary gonadal and lactotroph axis in the acute phase of TBI and SAH:

As demonstrated in table 7 and 8 suppression of the HP-gonadal axis is common in the acute phase of both TBI and SAH patients. Suppression of the HP-gonadal axis has even been reported in non-traumatic illness (106,107) and as previously discussed may be an adaptive response which though could be maladaptive in the chronically critically ill patient (60,61) and even as reported that low testosterone in male TBI patients when starting rehabilitation correlated with poorer rehabilitation (108)

1.5.7 Hypothalamic-pituitary thyroid axis in the acute phase of TBI and SAH:

As demonstrated in table 7 and 8 the incidence of thyroid deficiency is either reported as secondary thyroid deficiency or low T3 syndrome and the incidence varies for TBI 1,7-51,9% and SAH 0-22,7%. Furthermore the diagnosis of secondary in the acute settings is difficult as the pattern of thyroid function tests are similar as those observed in low T3 syndrome. As the value of thyroid hormone replacement is not proven the diagnosis of thyroid dysfunction may not be crucial in the early phase of TBI or SAH (105).

1.5.8 Hypothalamic-pituitary somatotroph axis in the acute phase of TBI and SAH:

As demonstrated in tables 7 and 8 the incidence of somatotroph deficiency in the acute phase of TBI is 18-41% and for SAH 12-22.7%. Only one of these studies that is Agha et al used a stimulation test and found an incidence of 18% (89). The clinical relevance of HP-somatoroph disturbance is unclear. Growth hormone replacement has been shown to improve mortality in burn patients (109) and even to increase mortality in surgery patients (110). As discussed previously IGF-1 has shown positive effects, in a TBI rat model, on cognitive and motor outcomes (27).

1.5.9 Pathophysiology of neuroendocrine disturbances in the TBI settings:

The pathophysiology of neuroendocrine dysfunction in the acute and chronic phase of TBI and SAH is not well understood. There are several mechanism following TBI and SAH that can cause injury to the hypothalamic-pituitary area including both primary and secondary injury. Skull fracture, mechanical damage through axonal shearing, hemorrhage with following oedema and increased ICP are all possible explanations as well as ischemic insults, hypoxia and hypotension, and vasospasm (66,111)

The anatomical position of the pituitary gland in the sella turcica make it vulnerable to mechanical trauma. Rotational and shearing injuries of the brainstem and fractures of the skull base and sella turcica may directly damage the pituitary, infundibulum or hypothalamus. This particularly affects the long hypophyseal vessels that lie in the infundibulum and provide the anterior pituitary gland with 70-90% of its blood supply (112). Autopsy series following TBI have shown injury to the hypothalamus, pituitary gland or infundibulum in 26-86% who died acutely following TBI and necrosis in the anterior pituitary was common (105,111,113–115). The fact that the somatotrophic and gonadotrophic axis are the most commonly affected in the chronic phase of TBI (66,69–73,80) supports the idea that hypopituitarism following TBI is partly vascular in origin as somatotroph cells are primarily located in the lateral wings of the anterior pituitary and the gonadotroph cells are scattered throughout the pars distalis and pars tuberalis of the anterior pituitary, areas vascularized by the long hypophyseal vessels that are susceptible to trauma. The thyrotroph and corticotroph cells are found in areas that are supplied by the less susceptible short hypophyseal vessels (112).

Neuroinflammation and the immune system might also play a role in hypopituitarism following TBI. Tanriverdi et al showed that TBI patients with antipituitary antibodies were more likely to suffer from hypopituitarism (116) and the same author has reported that APO-E3/E3 genotype decreases the risk of pituitary insufficiency. APO-E is an apolipoprotein within the central nervous system and it is up-regulated after injury. The authors speculate that individual variation in APO-E related mechanism may influence the pathogenesis of hypopituitarism following TBI (117).

1.5.10 Pathophysiology of neuroendocrine disturbances in the SAH settings:

There is a case report of hemorrhages in the pituitary following SAH (118). Furthermore in a autopsy study on the hypothalmus in SAH patients there was evidence of ishcemia and micro and macro hemorrhages in 68% of cases. It has been suggested that direct damage to the perforating hypothalamic arteries, which run from the subarachnoid space to the hypothalmus, may occur through

vasoconstriction causing ischemia and the forced transit of blood from the SAH through the perforating arteries with rupture of blood into the cerebral parenchyma (105,119).

There is also evidence that SAH affects the pituitary not just via physical damage from extravasated blood. The bleeding triggers a proinflammatory cascade which leads to complications of SAH. Cytokines, vasoactive factors and neuropeptides lead to a dissociation between ACTH and cortisol through altered sensitivity to ACTH (105,120).

2 Aims:

We conducted a prospective study with the aim to assess and describe the neuroendocrine changes in the acute phase of severe and moderate TBI and SAH. Furthermore to assess any association between the neuroendocrine changes and clinical and labarotory, S100b, variables indicating severity of insult. Conditions in Iceland are particularly favourable for studying prevelance on a national level. The population is small, numbering only 318.000 at the time of the study (Statistic Iceland, www.statice.is) inhabitants and all severe (Glasgow coma score (GCS) <9) TBI and all SAH as well as most moderate (GCS 9-12) TBI are transferred and treated at one hospital, LUH housing the only Neurosurgery Department in the country.

We aimed to investigate:

- The prevalence and nature of neuroendocrine disturbances during the acute phase mTBI and sTBI.
- The prevalence and nature of neuroendocrine disturbances during the acute phase SAH.
- Associations between neuroendocrine changes, during the acute phase of, mTBI and sTBI, and SAH, and clinical and labarotory variables.

3 Material and methods:

3.1 Subjects:

During the period March 2009 – March 2010 patients admitted to Landspitali – National University Hospital of Iceland (LUH) with TBI or SAH were considered for inclusion in the study. Inclusion criteria for TBI patients was age 18-70 years and moderate or severe TBI, judged by post resuscitation Glasgow coma score, <9 or 9-12 respectively. All patients with SAH were considered for inclusion with no age criteria or GCS score. LUH houses the only neurosurgery department in Iceland covering a region of approximetely 318.000 inhabitants at the time of the study (Statistic Iceland, www.statice.is)

During the 12 months period, 21 TBI patients were prospectively included on admission or shortly after, 6 moderate TBI and 15 severe TBI, 17 males and 4 females, median age 34 (47), mean age 34±13 years. TBI was caused by traffic accidents (car, bicycle and pedestrian) in 7 of the 21 patient, fall in 6 of the 21 patient, assault in 4 of the 21 patient and construction working accidents in 4 of the 21 patient. Four TBI patients were lost to follow up on day 6; 1 patient with sTBI died, 1 mTBI patient and two sTBI patients did not attend to follow up. One TBI patient missed testing at day 6 but was tested on day 9 post trauma. Those results are presented with day 6.

Nineteen patients with SAH were included, 12 males and 7 females, median age 56 (55), mean age 54±14 years (range 30-85 years). Fourteen SAH patients were included on admission but 5 at later stages because of patient delay as they did not seek medical help until days after the beginning of symptoms. Three patients with SAH were lost to follow up on day 6, all three had died during the first days. Three SAH patients were tested on day 8,10 and 14 respectively as they missed being tested on day 6. Those results are presented as results on day 6.

3.2 Ethics:

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of LUH. All participants or their closest of kin gave their written consent after receiving oral and written information about the study.

3.3 Anterior pituitary assessment:

Anterior pituitary function was assessed on admission, or as soon as informed consent had been acquired, by analyzing serum levels of cortisol, growth hormone (GH), insulin like growth factor1 (IGF-1), thyroid stimulating hormone (TSH), free thyroxine 4 (fT4), prolactin (PRL), luteinizing hormone (LH), follicle stimulating hormone (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 levels measured in the morning as close to 8 am as possible and additionally a Synacthen test was performed.

Synacthen test was performed by measuring serum levels of cortisol and p-ACTH at baseline followed by injection of tetracosactrin (Synachten) 250 mcg iv measuring cortisol 30 and 60 min after the injection.

In accordance with recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care, ACTH/cortisol deficiency was defined as a cortisol value of <276 nmol/L or an increase of >248 nmol/L after synacthen test (58).

Suggested somatotrophin deficiency was defined as subnormal age- and gender related IGF-1 value. Thyrotropin deficiency was defined as subnormal serum levels of fT4 with inappropriately low serum levels of TSH. Gonadotropin deficiency was defined as subnormal testosterone (in men) and inappropriately low serum levels of LH and FSH.

3.4 Analytic methods:

Overview of analytic methods is provided in table 7. Serum levels of fT4, TSH, progesterone, estradiol, PRL, total 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). IGF-1 was analyzed using a solid-phase, enzyme labeled chemiluminescent immunometri assay (IMMULITE/IMMULITE 1000, Siemens) and ACTH using a solid-phase, two site sequential chemiluminescent immunometric assay (IMMULITE/IMMULITE 1000, Siemens).

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

3.5 Clinical and laboratory variables as indicators of severity and ischemic events:

From patients chart we recorded the first post-resuscitation GCS for all patients, Hunt and Hess grade for SAH patients based on neurological examination att arrival, Injury severity score for TBI patients, an established medical score to assess trauma severity (121), APACHEII score (Acute Physiology and Chronic Health Evaluation II) for all patients, a severity-of-disease classification system (122), 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 2-24. Serum levels of S100b was measured with the first hormonal measurements.

3.6 Statistics:

All statistical analyses were performed by using IBM SPSS statistics version 20. Continous 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. To compare differences in hormone values within each group at different time points Wilcoxon signed rank test was used. To compare differences in continous variables between TBI and SAH groups Mann Whitney U was used. To compare differences in nominal variables between TBI and SAH group Fischer exact was used. To

compare difference in TBI and SAH 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 continous variables. Statistical significance was accepted at $p < 0.05$.

Table 9. Analytic methods

				Laboratory intra assay variability (CV%)					Specimen	
Analyte	Assay name	Manufacturer	Instrument	Low control	Median control	High control	Reportable range	Reference range	Type	Storage
TSH	TSH	Roche	Elecsys	4.0	3.4	3.5	0.005-100.00 mIU/L	0.3-4.2 mIU/L	Serum	+2-8 °C
Free T4	fT4	Roche	Elecsys	4.4	3.9	5.8	0.3-100 pmol/L	12-22 pmol/L	Serum	+2-8 °C
Cortisol	Cortisol	Roche	Elecsys	7.0	3.5	3.3	0.5-1750 nmol/L	170-700 nmol/L	Serum	+2-8 °C
Progesterone	Progesterone II	Roche	Modular E170	8.7	-	4.5	0.095-191 nmol/L	male 0.7-4.3 nmol/L; female 0.6- 4.7 nmol/L (follicular phase), 5.3- 86 nmol/L (luteal phase), 0.3-2.5 nmol/L(post-menopausal)	Serum	+2-8 °C
Estradiol	Estradiol II	Roche	Modular E170	6.5	-	5.5	18.4-15781 pmol/L	male 28-156 pmol/L; female 46- 607 pmol/L (follicular phase), 161- 774 pmol/L (luteal phase), <18.4- 201 pmol/L(post-menopausal)	Serum	+2-8 °C
Prolactin	Prolactin II	Roche	Modular E170	3.1	-	2.5	1-10000 µIU/L	male 4.5-21 µg/L ; female 5-30 µg/L	Serum	+2-8° C
Testosterone	Testosterone	Roche	Modular E170	6.4	-	4.6	0.069-52 nmol/L	male 9.9-27.8 nmol/L ; female 0.22-29 nmol/L	Serum	+2-8 °C

Cont. Table 7. Analytic methods

				Laboratory intra assay variability (CV%)					Specimen	
Analyte	Assay name	Manufacturer	Instrument	Low control	Median control	High control	Reportable range	Reference range	Type	Storage
FSH	FSH	Roche	Modular E170	2.8	-	2.5	0.1-200 mIU/L	male 1.5-12 U/L; female 3.5-12.5 U/L (follicular phase), 2-8 U/L (luteal phase), 26-135 U/L(post-menopausal)	Serum	+2-8 °C
LH	LH	Roche	Modular E170	2.4	-	2.0	0.1-200 mIU/L	male 1.7-9 U/L; female 2.4-12.6 U/L (follicular phase), 1-11 U/L (luteal phase), 7.7-58.5 U/L(post-menopausal)	Serum	+2-8 °C
S100b	S100b	Roche	Modular E170	0.26	-	3.33	0.005-39 µg/L	<0.105 µg/L	Serum	+2-8°C
IGF-1	IGF-1	Siemens	Immulite 1000	9.4	-	7.0	Up to 1600 ng/L	Manufacturer´s age dependent reference range *	Serum	-20 °C
ACTH	ACTH	Siemens	Immulite 1000	9.9	-	7.0	Up to 1250 pg/ml	< 46 ng/L	EDTA-Plasma	-20 °C
GH	Growth hormone (hGH)	Siemens	Immulite 1000	3.4	4.2	3.0	Up to 96 mIU/L	0.1-11.5 mIU/L	Serum	-20 °C
GH	Growth hormone (hGH)(Recombinant 98/574)	Siemens	Immulite 1000	5.1	4.4	4.9	0.05-40 µg/L	male < 3.0 µg/L ; female < 8 µg/L	Serum	-20 °C

CV = Coefficient of variability, contr. = control, TSH = thyroid stimulating hormone, FT4 = free thyroxine, FSH = follicle stimulating hormone, LH = luteinizing hormone, IGF-1 = Insulin-like growth factor 1, ACTH = Adrenocorticotropic hormone, GH = growth hormone.*) Immulite product booklet, IGF-1, Immulite 1000 IGF-1 (PILKGF-10, 2006-12-29).

4 Results:

During the 12 months period 21 TBI patients were prospectively included in the study, 6 moderate TBI and 15 severe TBI, 17 males and 4 females, mean age 34±13 years (range 18-65 years). TBI was caused by traffic accidents (car, bicycle and pedestrian) in 7 of 21 patients, fall in 6 patients, assault in 4 patients and construction working accident in 4 of the patients. Mean GCS for TBI patients was 6.7±3.5 (range 3-12), mean Injury severity score was 24.3±16.8 (range 0-57), mean APACHEII score was 13.2±7.4 (range 0-26), mean length of ICU stay 5.3±6.3 (range 0-26) and 9 of the 21 patients were intoxicated by alcohol at the time of trauma. Demographics and the above clinical variables are demonstrated in table 8.

Twenty-one TBI patient were included on admission or shortly after admission. Four TBI patients were lost to follow up on day 6, one of these four patients a patient with severe TBI died, the remaining three lost to follow, one with moderate TBI and two with severe TBI, judged by GCS, were discharged from the hospital before day 6 and did not attend to the offered follow up. One TBI patient missed testing at day 6 but was tested on day 9 post trauma. Those results are presented with day 6.

Nineteen patients with SAH were included, 12 males and 7 females, mean age 54±14 years (range 30-85 years). Mean GCS for SAH patients was 11.1±5.2 (range 3-15), mean Hunt and Hess score was 3.0±1.3 (range 1-5), mean APACHEII 13.1±10.2 (range 0-35), mean length of ICU stay 5.0±10.2 (range 0-17). Fourteen SAH patients were included on admission and 5 SAH patients were included at later stages because of patient delay as these patients did not seek medical help until days after the beginning of symptoms. Three patients with SAH died before day 6 and were thus lost to follow up. Three SAH patients were tested on day 8, 10 and 14 respectively as they missed being tested on day 6. Those results are presented as results for day 6.

Mean and median hormone values on admission and day 6 for the TBI and SAH group are presented in tables 8 and 9 respectively. Proportion of both TBI and SAH patients on admission and day 6 with low, normal or high hormone values are presented in figure 4 and 5.

Overview of TBI or SAH patients with documented the occurrence of pupil dilatation or documented ischemic event that is the occurrence of documented serum haemoglobin level (Hb) below 80 g/dl, the occurrence of hypotension defined as a recorded systolic blood pressure (SBP) <90 mmHg or hypoxia defined as a recorded SpO2<90% during the first hour post insult or hours 2-24 post insult is demonstrated in table 8.

Table 10. Demographics and mutual clinical variables for TBI and SAH groups

	TBI	**SAH**	**p-value**
Age	34 (47) 34.43 ±2.75	56 (55) 54.16 ±3.23	***p=0.000****
Gender	4 female; 17 male	7 female, 12 male	p=0.293
GCS	7 (9) 6.71 ±0.75	14 (12) 11.11 ±1.19	***p=0.003****
APACHEII	14 (26) 13.24 ±1.61	11 (35) 13.11 ±2.41	p=0.646
Length of ICU stay	3 (26) 5.33 ±1.38	5 (17) 5.00 ±1.04	p=0.707
S100b	0.33 (6.58) 0.83 ±0.33	0.13 (0.23) 0.12 ±0.16	***p=0.004****
Dilatation of pupil	19.0% (4/21)	15.8% (4/19)	p=1.0
Systolic BP <90 mmHg, 1st hour	19.0 % (4/21)	5.3% (1/19)	p=0.349
Systolic BP<90 mmHg, hours 2-24	47.7% (10/21)	42.1% (8/19)	p=1.0
SpO2 < 90%, 1st hour	4.8% (1/21)	5.3% (1/19)	p=1.0
SpO2 < 90%, hours 2-24	9.5% (2/21)	15.8% (3/19)	p=0.640
Hemoglobin <80g/dL	9.5% (2/21)	0% (0/19)	p=0.490

TBI = traumatic brain injury, SAH = subarachnod hemorrhage, GCS = Glasgow coma scale, APACHEII = Acute Physiology and Chronic Health Evaluation II, ns = non-significant. Data is presented as median (range) and mean±SEM.

Table 11. Mean and median hormone values on admission and day 6, TBI group

	Reference range	Day 0	N	Day 6	N	p-value
TSH	0.3-4.2 mIU/L	1.77±0.34 1.11 (5.85)	21	2.20 ±0.32 2.30 (4.77)	17	p=0.149
fT4	12-22 pmol/L	15.36±0.70 15.75 (13.00)	21	14.49±0.60 14.7 (11.50)	17	p=0.776
LH (male)	male 1,7-9 U/L	5.28±1.41 4.05 (23.70)	16	2.96±0.65 2.1 (7.00)	13	p=0.289
FSH (male)	male 1,5-12 U/L	4.66±0.82 3.50 (11.30)	17	2.04±0.61 1.70 (8.60)	13	***p=0.003 ****
Testosterone (male)	9.9-27.8 nmol/L	10.85±2.09 7.95 (26.19)	16	6.01±2.35 2.20 (30.30)	13	p=0.055
ACTH	< 46 ng/L	72.85±22.06 23.0(369.0)	20	43.50±10.88 29.0 (148.0)	16	p=0.730
Cortisol	170-700 nmol CIRCI<276nmol	633.76±75.74 723.0(1086.0)	21	650.80±71.9 585.0 (1086.0)	17	p=0.733
Prolactin	male 4.5-21 ug/L ; female 5-30 ug/L	24.78±4.19 18.80 (78.0)	21	15.98±1.58 16.40 (23.60)	17	p=0.237
IGF-1	* age related	117.62±13.45 98.0 (258.0)	21	192.35±20.23 168.0 (302.0)	17	***p=0.000****

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. TSH = thyroid stimulating hormone, fT4 = free thyroxine, LH = luteinizing hormone, FSH = follicle stimulating hormone, ACTH = adrenocorticotroph hormone, IGF-1 = Insulin growth factor 1, ns = non significant

* IGF-1 age-dependent reference range (µg/l); 18 years(y) : 163-584, 19y: 141-483, 20y: 127-424, 21-25y: 116- 358, 26-30y: 117-329, 31-35y: 115-307, 36-40y: 109-284, 41-45y: 101-267, 46-50y: 94-252, 51-55y: 87-238, 56- 60y: 81-225, 61-65y: 75-212, 66-70y: 69-200.

Table 12 Mean and median hormone values on admission and day 6, SAH group

	Reference range	**Day 0**	**N**	**Day 6**	**N**	**p-value**
TSH	0.3-4.2 mIU/L	1.51 ±0.38 1.07 (5.57)	14	2.12±0.44 1.63 (5.61)	16	p=0.091
fT4	12-22 pmol/L	17.96±0.59 17.45 (8.00)	14	15.31±0.58 15.65(7.80)	16	***p=0.041****
LH	male 1,7-9 U/L	4.88 ±0.91 5.10 (8.90)	9	4.19±0.85 3.95 (8.70)	10	p=0.735
FSH	male 1,5-12 U/L	6.52 ±1.38 6.2 (13.40)	9	4.67 ±1.24 3.50 (12.30)	10	***p=0.034****
Testosterone (male)	9.9-27.8 nmol/L	9.64 ±2.70 6.80 (25.90)	9	3.70 ±1.20 2.30 (12.06)	10	p=0.128
ACTH	< 46 ng/L	173.5±86.5 48.0(1039.0)	14	29.67±5.88 27.0(55.0)	14	p=0.463
Cortisol	170-700 nmol CIRCI<276nmol	1428.8±357.0 1056.0(5104.0)	14	623.5±66.09 661.0(690.0)	16	p=0.128
Prolactin	male 4.5-21 ug/L ; female 5-30 ug/L	20.00 ±3.00 23.05 (31.30)	14	11.58 ±2.18 9.00 (36.5)	16	p=0.091
IGF-1	*age related	91.00±6.76 98.0 (99.0)	14	119.63±12.32 96.5(162.0)	16	p=0.333

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). TSH =thyroid stimulating hormone, fT4 = free thyroxine 4, LH = luteinizing hormone, FSH = follicle stimulating hormone, ACTH = adrenocorticotroph hormone, IGF-1 = Insulin growth factor 1, ns = non significant

* IGF-1 age-dependent reference range (µg/L); 18 years(y) : 163-584, 19y: 141-483, 20y: 127-424, 21-25y: 116- 358, 26-30y: 117-329, 31-35y: 115-307, 36-40y: 109-284, 41-45y: 101-267, 46-50y: 94-252, 51-55y: 87-238, 56- 60y: 81-225, 61-65y: 75-212, 66-70y: 69-200.

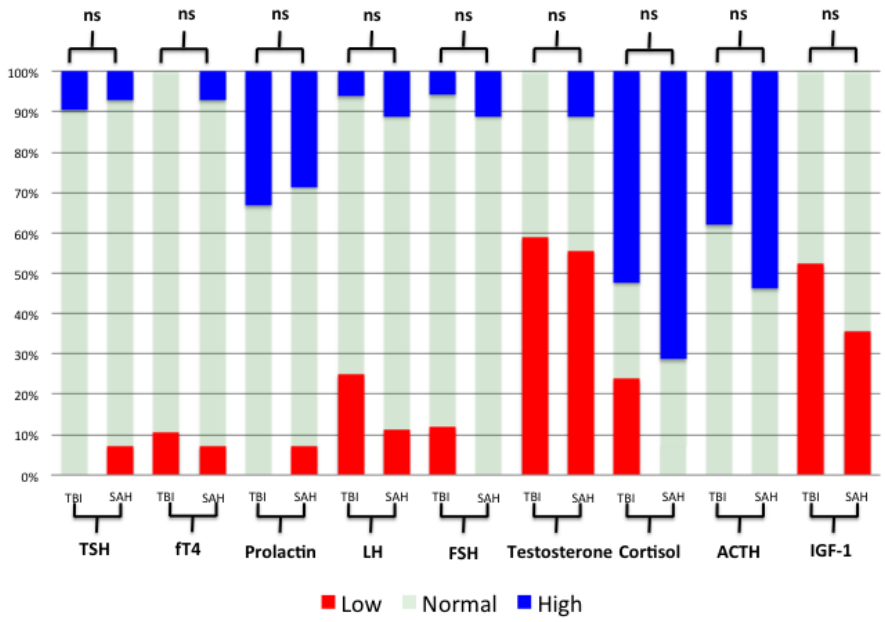

Figure 4 Proportion of both TBI and SAH patients on admission with low, normal or high hormone values TSH =thyroid stimulating hormone, fT4 = free thyroxine 4, LH = luteinizing hormone, FSH = follicle stimulating hormone, ACTH = adrenocorticotroph hormone, IGF-1 = Insulin like growth factor 1

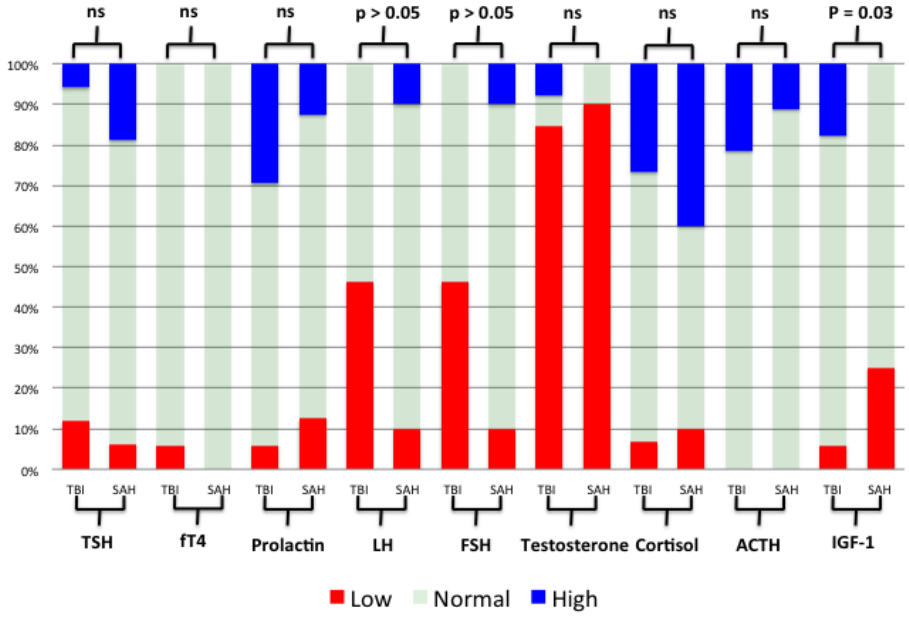

Figure 5 Proportion of both TBI and SAH patients on day 6 with low, normal or high hormone values TSH =thyroid stimulating hormone, fT4 = free thyroxine 4, LH = luteinizing hormone, FSH = follicle stimulating hormone, ACTH = adrenocorticotroph hormone, IGF-1 = Insulin like growth factor 1

4.1 Hypothalmic-pituitary adrenal axis:

On admission TBI patients had significantly lower cortisol levels compared to SAH patients, 633.8 nmol/L±75.74 vs. 1332.6 nmol/L ±344.2, U =76, Z -2.392, p = 0.016. The mean ACTH in the TBI group was lower although not significant. There was no significant difference on day 6.

One SAH patient had received corticosteroids before blood samples were drawn on admission. Two TBI patients and 7 SAH patients received treatment with corticosteroids the first 6 days. These patients are excluded in calculations although mentioned below.

On admission 5 of 21 (23.8%) TBI patients had cortisol levels below the proposed limit for critical illness related corticosteroid insufficiency (CIRCI) [20] of cortisol<276 nmol/L and concomitant low 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%) TBI patient had cortisol levels below cut-off at 276 nmol/L, the patient had cortisol of 155 nmol/L and ACTH <10 ng/L. That patient had a normal response on the synacthen test. Two patients had received treatment with corticosteroids. One of them had received treatment with dexamethasone and had cortisol levels of 10 nmol/L and concomitant low levels of ACTH <10 ng/L. That patient failed the synacthen test with a maximal response of 356 nmol/L. He was treated with corticosteroids and retested on day 19 and then had a normal Synacthen test. The other patient treated with cortisone had normal levels of cortisol and a normal response on the Synacthen test. Two TBI with high cortisol levels were not tested with a Synacthen test on day 6. All other TBI patients underwent a Synacthen test and showed a normal response.

Only 1 of 14 (7,1%) SAH patient had low cortisol levels on the first blood sample and that patient had already received corticosteroids complicating interpretation thus no patient had low cortisol when excluding those who had received corticosteroid treatment. On day 6, 1 of 11 (9,1%) had cortisol levels below cut-off at 276 nmol/L, the patient had cortisol of 270 nmol/L and ACTH 48 ng/L and showed a normal response on synacthen test.

As shown in figures 4 and 5 there was no significant difference in the proportion of patients with low, normal or high cortisol in the TBI vs. the SAH group. There was no significant difference either when proportions of patients with low or not low was compared between TBI and SAH groups.

In the TBI group there was a positive correlation between cortisol on day 0 and LH on day 0, rho = 0.725, p = 0.001 and a positive correlation between ACTH on day 0 and LH on day 0, rho = 0.578, p = 0.019. Correlation between FSH and cortisol was not significant (rho = 0.419, p= 0.094) and neither between ACTH and FSH (rho = 0.470, p = 0.057). No such correlation was found in the SAH group.

4.2 Hypothalmic-pituitary gonadal axis:

4.2.1 Hypothalamic-pituitary gonadal axis in males:

Testosterone was the most commonly affected hormone in both TBI and SAH patients with median levels lower than normal values in both groups on admission and day 6 as shown in tables 9 and 10. Furthermore there was a significant decrease in FSH levels in both groups between admission and day 6 and a trend to lower LH levels. FSH was significantly lower in the TBI group compared to the

SAH group on day 6, 2.04 U/L ±0.61 vs. 4.67 U/L ±1.24, U = 28.5, Z = -2.266, p = 0.021. Furthermore there was a significant difference in the proportion of patients with abnormal LH and FSH that is values outside the reference range, on day 6 between the two groups see figure 5.

On admission 9 of 17 (52.9%) male TBI patients had low testosterone levels below lower reference value. Of these patients two had concomitant levels of LH and FSH below lower reference value and two had low LH and FSH low but within normal range. On day 6, 11 of 13 (84.6%) male TBI patients had low testosterone levels. Of the patients with low testosterone levels 4 (30.8%) had concomitant low levels of both LH and FSH, 2 had low LH and FSH low but within normal range, 2 with low FSH and LH low but within normal range.

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

4.2.2 Hypothalamic-pituitary gonadal axis in females:

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 as this made any interpretation unreliable.

4.3 Hypothalmic-pituitary lactotrophic axis:

Prolactin showed similar trends in both TBI and SAH group with high levels on admission and a trend to decreasing levels on day 6. Prolactin was significantly higher on day 6 in the TBI group compared to the SAH group, 15.98 ±1.58 vs. 11.58 ±2.18, U = 74.00, Z = -2.234, p = 0.025.

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

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

There was no significant correlation between prolactin levels and LH, FSH or testosterone levels.

4.4 Hypothalmic-pituitary thyrotrophic axis:

Mean and median TSH and fT4 remained within reference range in both TBI and SAH group on admission and day 6. In the SAH group fT4 levels on day 6 compared to admission had significantly decreased from 17.96 ±0.59 to 15.31 ±0.58, p = 0.04. There was no significant change in fT4 levels in the TBI group. There was no significant change in TSH in neither the TBI nor the SAH group. Serum levels of fT4 were significantly higher in the SAH group compared to TBI group on admission 17.96 ±0.59 vs. 15.36 ±0.70 respectively, U = 74.50, Z = -2.442, p = 0.13.

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 patient in the TBI group had values compatible with primary hypothyroidism on

admission with high levels of TSH and low levels of fT4. That patient did not have known hypothyroidism earlier and on day 6 the fT4 levels were within reference range but TSH levels still high. Another patient had low levels of fT4 with normal TSH levels on admission but normal levels on day 6. The third patient had high levels of TSH with low levels of fT4 on admission and on day 6 low levels of fT4 with low levels of 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 TSH levels with normal fT4 levels on admission but normal values on day 6. One patient had low fT4 value with normal TSH on admission but on day 6 normal fT4 levels with high TSH value. The third patient had normal values on admission but on day 6 low value of TSH with normal fT4 value.

4.5 Hypothalmic-pituitary somatotrophic axis:

Because of age related reference range and the demographic differences in the TBI and SAH group comparison of mean IGF-1 is not feasible. There was however a difference in changes in IGF-1 between groups. There was a significant increase in IGF-1 levels on day 6 in the TBI group compared to admission as levels increased from 117.62 ±13.45 to 192.35 ±20.23, p >0.01. There was no significant change between admission and day 6 in the SAH group and the median level decreased 98.5 (range 99.0) to 96.6 (range 162.0). There was a significant difference in the proportion of patient with IGF-1 values out of normal range on day 6 between the two groups with lower proportion of low IFG-1 and higher proportion with high IGF-1 in the TBI group as shown in figure 2.

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

On admission 5 of 14 (35,7%) SAH patients had abnormally low IGF-1 levels. On day 6, 4 of 16 (25.0%) SAH patients had low levels of IGF-1, three of the patients with low levels on admission still had low levels of IGF-1 and one patient included after admission had low levels of IGF-1 on day 6. Two patients with low levels on admission had normalized their IGF-1 levels.

GH was even measured. The analytic method was changed during the study period and since single GH measurements are of little value those results are not presented.

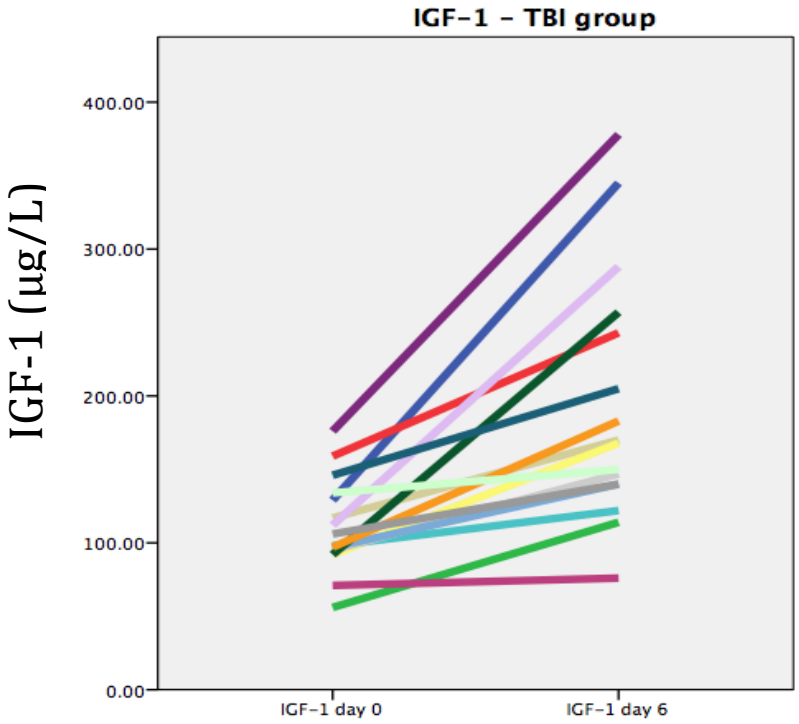

Figure 6 Changes in Insulin like growth factor 1 (IGF-1) in the TBI group from admission to day 6, each line represents one patient

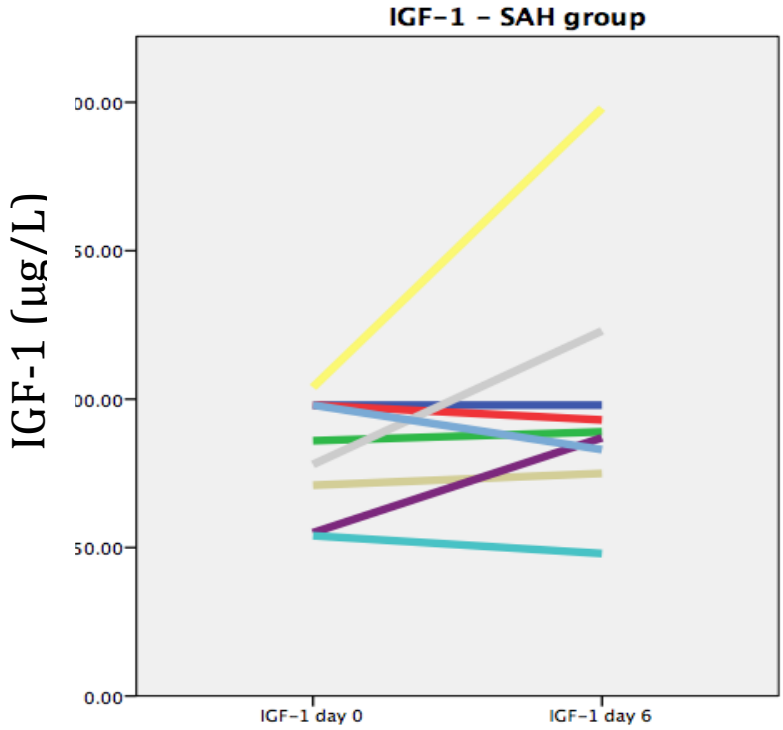

Figure 7 Changes in Insulin like growth factor 1 (IGF-1) in the SAH group from admission to day 6, each line represents one patient.

4.6 Correlations between hormone values and indicators of severity:

Overview of significant correlation between variables used as indicators of severity and hormone values, on admission and day 6, is provided in tables 10 and 11.

Overview of significant differences in hormone values of TBI or SAH patients with documented the occurrence of pupil dilatation, documented ischemic event that is the occurrence of documented serum haemoglobin level (Hb) below 80 g/dl, the occurrence of hypotension defined as a recorded systolic blood pressure (SBP) <90 mmHg or hypoxia defined as a recorded SpO2<90% during the first hour post insult or hours 2-24 post insult is presented in tables 12 and 13.

Table 13 Overview of significant correlation between variables, indicators of severity, and hormone values in TBI patients

Clinical variable	Hormone	Spearman's rho	p value
GCS	TSH day 6	0.547	0.023
GCS	fT4 day 0	-0.557	0.009
GCS	FSH day 0	-0.594	0.012
GCS	testosterone day 0	-0.57	0.021
ISS	fT4 day 0	-0.484	0.026
ISS	cortisol day 6	0.561	0.030
S100b	cortisol day0	0.538	0.012

GCS = Glasgow coma scale, ISS = Injury severity score, TSH = thyroid stimulating hormone, fT4 = free thyroxin 4.

Table 14 Overview of significant correlation between variables, indicators of severity, and hormone values in in SAH patients

Clinical variable	Hormone	Spearman's rho	p value
GCS	fT4 day6	0.522	0.038
Hunt and Hess	fT4 day 6	-0.628	0.009
APACHEII	fT4 day 6	-0.540	0.038
Length of ICU stay	fT4 day 0	-0.546	0.044
Length of ICU stay	testosterone day 6	-0.797	0.010

GCS = Glasgow coma scale, APACHEII = Acute Physiology and Chronic Health Evaluation II, fT4 = free thyroxin 4

Table 15: Significant differences in hormone values grouping TBI whether dilatation of pupil or ischemic event occurred or not

Event	Yes to event	No to event	p value
Dilatation of pupil	TSH day 6, mUl/L 0.50 ± 0.31 0.34 (1.05)	TSH day 6, mUl/L 2.56 ± 0.30 2.58 (4.58)	0.012
Systolic BP < 90 mmHg, 1st hour	ACTH day 0, ng/L 149.75 ± 46.22 166.0 (221)	ACTH day 0, ng/L 53.63 ± 23.26 13 (369)	0.029

Hormone values and S100b presented as mean ± SEM and median (range). TSH = thyroid stimulating hormone, ACTH = adrenocorticotrophic hormone, Hb = hemoglobin.

Table 16: Significant differences in hormone values grouping SAH patients whether dilatation of pupil or ischemic event occurred or not

Event	Yes to event	No to event	p value
Dilatation of pupil	Testosterone day 0, nmol/L 18.27 ± 5.17 15.8 (17.4)	Testosterone day 0, nmol/L 5.33 ± 1.00 5.45 (6.65)	0.024
Systolic BP < 90 mmHg, hours 2-24	Testosterone day 0, nmol/L 17.65 ± 5.63 15.8 (19.25)	Testosterone day 0, nmol/L 5.63 ± 1.24 5.45 (8.50)	0.048
Systolic BP < 90 mmHg, hours 2-24	ACTH day 0, ng/L 235.8 ± 163.8 89.0 (1040)	ACTH day 0, ng/L 118.9 ± 87.2 42.0 (630)	0.03
Saturation < 90%, hours 2-24	PRL day 6, ug/L 21.13 ± 8.37 14.2 (26.4)	PRL day 6, ug/L 9.37 ± 1.57 8.0 (20.8)	0.022

Hormone values presented as mean ± SEM and median (range). TSH = thyroid stimulating hormone, ACTH = adrenocorticotrophic hormone, Hb = hemoglobin.

5 Discussion:

In this prospective study we described and compared neuroendocrine changes in the acute phase of moderate and severe TBI and SAH on admission and 6 days post insult. We investigated association between hormone values and possible predictive factors.

In summary we found neuroendocrine disturbances to be common in both the acute phase of TBI and SAH. The HP-adrenal axis was affected in 23.8% of TBI group on day 0 and 6.7% on day 6. The HP-adrenal axis was affected in only one SAH patient, 9.1%, and that was on day 6. The HP-gonadal axis was the most commonly affected HP-axis. On day 6 the HP-gonadal axis was affected in 84.6% of male TBI patients and 90% of male SAH patients. The HP-thyroid axis was the least affected HP-axis and only one TBI patient, 5.9%, had TSH and fT4 levels compatible with secondary hypothyroidism and none in the SAH group. The HP-somatotroph axis was affected in 52.4% of the TBI patients on day 0 but had mostly resolved on day 6 compared to 35.7% of the SAH group on day 0 and 25.0% on day 6. In general when evaluating association there seemed to be more suppression of the thyroid axis with more severe insult and adequately more activation of the hypothalamic-pituitary adrenal axis. The association between severity and the hypothalamic-pituitary-gonadal was conflicting with more severe insult having less suppression on admission but on day 6 there was a strong negative correlation between testosterone and length of ICU stay in the SAH group. We did not identify any good predictive factor for neuroendocrine disturbance in the acute phase of TBI and SAH.

5.1 Hypothalmic-pituitary adrenal axis:

Diagnosing a true clinically relevant cortisol deficiency in the acute settings of any critical care patient is challenging but at the same time, the most important hormone deficiency to diagnose and treat with a stress dose of glucocorticoids. The American College of Critical Care recommendations from 2008 on the diagnosis and management of critical illness related corticosteroid insufficiency (CRCI) sets the cut-off value for serum cortisol level at less than 276 nmol/L or an increase of less than 248 nmol/L after Synacthen test. CRCI should be suspected in hypotensive patients who have responded poorly to fluids and vasopressor agents (58). Relying solely on Synacthen test is not recommended since in the case of pituitary failure the adrenals may still respond up to 6 weeks after pituitary failure (105). The adrenal may even respond to the high dose of Synacthen and show a response despite the adrenals being resistant to endogenous ACTH. Furthermore the cut-off value for the diagnosis of CICR is still much debated and even which supplemental doses of hydrocortisone should be used (123).

We found on admission that 23.8% of the TBI group (n=21) had cortisol levels suggestive of CRCI but on day 6, only one TBI patient (6.7% of the TBI group) had low serum cortisol. The mean cortisol level was significantly lower in the TBI group compared to the SAH group, 634 nmol/L ±75.7 vs. 1333 nmol/L ±344, ($p = 0.016$). Only one SAH patient (9.1% of the SAH group) had marginally low serum cortisol on day 6, 270 nmol/L and a normal Synacthen test.

Previous studies have shown different incidence of corticotroph dysfunction that certainly is partly explained by different methodology and definitions. There are studies showing both higher and lower

incidence (70,91,93,95,96). Our results for the TBI group are in line with the study of Kleindienst et al on TBI, which used similar definitions as in our study setting the cut-off value for cortisol at 290 nmol/L (92). Tanriverdi et al used even more stringent baseline cortisol value and found lower incidence. Olivecrona et al reported a higher incidence at day 1 and day 4 (96) and it is possible that the difference lies in that in our study the measurements are done at time points earlier, on day 0, and then later, on day 6 post insult. The low incidence Klose et al found, might be due to the use of Synacthen test for diagnosis (70). We only used the Synacthen test on day 6.

Published studies on the HP-adrenal axis in the acute phase of TBI are inconsistent. There is conflicting data on the association between cortisol levels and clinical outcome. Hannon et al found patients with hypocortisolemia to have longer ICU stay and patients in the lowest quartile of mean cortisol levels and those with low serum cortisol on day 10 post insult had higher mortality (95). Olivecrona et al on the other hand, reported a higher mortality at 3 months for patients with higher cortisol levels in the acute phase (96)

Cortisol deficiency and abnormality in diurnal cycle of cortisol in SAH patients are associated with worse outcome (100,102). Perhaps the association between cortisol and worse outcome is explained by the fact that patients with lower levels of cortisol have possibly had a more severe insult.

As mentioned above we found a significant difference in cortisol values between the TBI and the SAH group on day 0. Whether that difference is because of TBI patients inadequately responding thus having what sometimes is called relative adrenal insufficiency or SAH producing a stronger sympathetic response is unknown. The difference could even lie in different treatment of these groups. The TBI group had significantly lower GCS and thus are more likely to be sedated. High dose propofol and thiopentothal has been shown to be associated with lower cortisol levels (91). One patient in the TBI group was treated with dexamethasone and was therefore excluded for day 6 follow-up, and had low cortisol levels and failed the Synacthen test. He was treated with hydrocortisone and re-tested on day 19 post insult and then had normal levels of cortisol and a normal Synacthen test. He was excluded from our calculations, except on day 0. Diagnosing that patient with CRCI would be questionable as dexamethasone suppresses cortisol production at least 6-8 hours and up to 48 hours (124).

In our study we found a positive correlation in the TBI group between serum cortisol on day 0 and S100b and serum cortisol on day 6 and Injury severity score (ISS). Documented hypotension in the 1st hour in TBI patients and hours 2-24 in the SAH group were associated with higher ACTH levels. This seems like an adequate response with higher cortisol levels in more severely injured patients. Failure to increase cortisol secretion could result in increased mortality as demonstrated by Hannon et al (95). Interestingly in the TBI group LH correlated with cortisol on admission (rho = 0.725, p = 0.001) and ACTH on admission (rho = 0.578, p = 0.019). The same trend in correlation although not significant was between FSH and cortisol (rho = 0.419, p= 0.094) and ACTH and FSH (rho = 0.470, p = 0.057). This might reflect a disturbance in the hypothalamic-pituitary area causing disturbances simultaneously in the HP-adrenal and HP-gonadal axis.

Treatment with corticoids in the acute phase of brain injury should be differentiated into replacement therapy for corticosteroid insufficiency for the truly deficient patient and pharmacological

treatment as a part of neuroprotective treatment. The CRASH trial showed an increase in mortality with corticosteroid treatment but in that trial TBI patients received supra-physological doses of methylprednisolone (125). The CRASH 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 (126). A Cochrane review on corticosteroid treatment in the acute phase of SAH was inconclusive (127)

It is clear from the discussions above that previous studies show conflicting results. This research field is complicated by diverse factors one being confounding factors with intensive care treatment as evident from Cohan et al research showing that high dose propofol and pentobarbital was associated with lower cortisol levels (Cohan et al., 2005). Furthermore based on our results it is clear that there is less activation of the HP-adrenal axis in TBI compared to SAH patients and relatively common for TBI patients to have cortisol values suggestive of CRCI. Diagnosing and treating true HP-adrenal deficiency is life saving and there is much need for further studies in this field.

5.2 Hypothalmic-pituitary gonadal and lactotroph axis:

As explained in the result chapter females were excluded from our evaluation of the HP-gonadal axis due to uncertainty of where in the menstrual cycle the women were and whether they were pre- or postmenopausal. Thus the discussions below is based on our results on male patients, on day 0, n=17 in the TBI group, n=9 in the SAH group, on day 6 n = 13 in the TBI group and n = 10 in the SAH group.

The HP- gonadal axis was the most commonly affected axis. On day 6, 84.6% of male TBI patients and 90.0% of male SAH patients had low testosterone values. That is in line with previous studies consistently showing strong suppression of the HP-gonadal axis in the acute phase of both TBI and SAH as well as critical illness in general. This is considered an adaptive response where the body is reducing energy consumption and conserving substrates for more vital functions (51,105). But nevertheless, this might indicate a lasting insufficiency in the HP-gonadal axis in some patients and therefore indicates the importance of further follow up of the pituitary hormones later on.

We found a stronger suppression at the pituitary level in the TBI group compared to the SAH group. At day 6 FSH levels were significantly lower in the TBI group vs. the SAH group, 2.04 U/L ±0.61 vs. 4.67 U/L ±1.24, p=0.021 and a trend to lower LH on day 6 2.96 ± 0.65 vs. 4.19 ± 0.85, p=0.203. Furthermore there was a significant difference between the TBI group and SAH group in the proportion of patients with LH and FSH outside reference range, high or low, on day 6 ($p<0.05$). 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 with the primary injury in traumatic brain injury with direct mechanical damage such as axonal shearing affecting the hypothalamic-pituitary area directly and immediately or early after the trauma whereas other proposed mechanism like ischemia caused by oedema and increased ICP takes more time to develop.

Interestingly we found a negative correlation between GCS and FSH, and GCS and testosterone, on day 0, rho=-0.594, p=0.012 and rho -0.57, p=0.021 respectively, meaning that more severe TBI assessed by the GCS had higher levels of FSH and testosterone. Furthermore in the SAH group patients who dilated a pupil had higher testosterone compared to those who did not dilate a pupil,

testosterone day 0 18.27 ± 5.17 nmol/L vs. 5.33 ± 1.00 nmol/L, p=0.024. Patients with a documented hypotension at hours 2-24 had higher testosterone levels compared to those who did not have a documented hypotension, 17.65 ± 5.63 nmol/L vs. 5.63 ± 1.24 nmol/L, p=0.048. This is difficult to explain and in contrary to previous studies on TBI patients (69)(92). Olivecrona et al did though find that low levels of testosterone, LH and FSH on day 1 was associated with increased survival 3 months post insult and low level of LH day 1 was associated with better outcome on GOS 3 months post insult. The authors hypothesize that more severe brain injury may hamper the physiological suppression of the HP-gonadal axis (96). There could be other confounding factors involved.

We found at strong negative correlation between testosterone levels on day 6, in the SAH group and length of ICU stay, rho=-0.797, p=0.010, and that is in line with previous studies showing more suppression with increased severity.

As expected, prolactin levels were generally high on day 0, also in line with previous studies. (89)(90)(69,79)(70,76)(93,96,92)(101) Tanriverdi et al found a negative correlation between serum prolactin and GCS (69). We did not find this correlation. Neither did we find a correlation between prolactin levels and testosterone, LH nor FSH levels.

We did not present results on the HP-gonadal axis in females nor did we measure estradiol or progesterone in males. Estradiol and progesterone have both been shown to be potential agents in neuroprotective therapy (27). Bearing that in mind it would be interesting to see whether endogenous levels of estradiol and progesterone correlate with outcome. Furthermore low testosterone levels in the beginning of rehabilitation have been correlated to less favorable outcome (108). The question is whether low serum testosterone identifies patients with the least rehabilitation potential or whether low testosterone levels per se halter rehabilitation.

5.3 Hypothalmic-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 fT4 and TSH serum levels below reference range (89,93,96,99). Other studies have reported higher prevalence of HP-thyroid disturbances have mainly reported low T3 syndrome which was not evaluated in our study (69,76,79).

We did find a significant decrease in fT4 level in the SAH group from day 0-6, 17.96 ±0.59 pmol/L to 15.31 ±0.58 pmol/L, p = 0.04 which is in line with previous studies which have shown a reduction in both fT4 and TSH levels with time in TBI and acute illness (96)(128). Small sample size could be one reason for us not detecting a significant change in fT4 level in the TBI group and TSH in both groups.

In the TBI group we found a positive correlation between TSH levels on day 6 and GCS, rho=0.547, p=0.023, and a negative correlation between fT4 levels on day 0 and ISS, rho=-0.484, p=0.026. In the SAH group we found a positive correlation between fT4 levels on day 6 and GCS, rho=0.522, p=0.038, a negative correlation between fT4 levels on day 6 and Hunt and Hess, rho=-0.628, p=0.009, APAHCEII and length of ICU stay, rho=-0.540, p=0.038. This 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 (92)(128)(96)(52). Surprisingly, we found a negative

correlation between fT4 levels on day 0 and GCS, rho=-0.557, p=0.009 which is conflicting with the above and difficult to explain. The small size of our group can of course be a contributing factor.

5.4 Hypothalmic-pituitary somatotroph axis:

Single measurements of growth hormone are of little value and added little to our results and were not presented.

On admission there was not a significant difference in the proportion of patients with IGF-1 levels outside age related reference range in the TBI and the SAH group with 52.4% of the TBI group having IGF-1 levels below age related normal values and 35.7% of the SAH group. On day 6 almost all TBI patients had normalized serum IGF-1 and even had higher than normal values whereas there was no significant change in IGF-1 in the SAH group with 25.0% still having low values on day 6. Our results for the TBI group are in accordance with previous studies from Olivecrona et al and Tanriverdi et al (96)(69). However, Kleindienst et al did not see as much restoration of IGF-1 levels on day 7 in a group of TBI patients. Regarding the SAH group previous studies have shown similar prevalence of low IGF-1 (79,99). Bendel et al measured serum IGF-1 on days 1-7 post SAH and on day 1, 77% had low IGF-1, and on day 7, 76% had low IGF-1 levels. They even reported association between lower IGF-1 level and poorer outcome measured with a quality of life questionnaire, HRQoL (98). The difference in changes in IGF-1 levels between TBI and SAH group could be the result of the TBI group being significantly younger and thus restoring their IGF-1 values more rapidly or there might be some difference in the insult per se causing low IGF-1 levels. Causes for low IGF-1 levels include GH insufficiency, decreased liver production or a decrease in IGF-1 caused by stress following critical illness (98).

IGF-1 has neurotropic effects, affects neuronal apoptosis and neuromodulation. As previously mentioned low levels of IGF-1 are associated with poorer QoL so levels of IGF-1 can play a role in the neurological recovery following TBI and SAH. Furthermore IGF-1 treatment has shown promising effect on cognitive and motor outcome in a TBI rat model (27). Thus IGF-1 and possibly GH might be potential therapeutic agents in the recovery after TBI and SAH. Still conflicting results have been reported on growth hormone treatment as it has been shown to improve mortality in burn patients (Knox, Demling, Wilmore, Sarraf, & Santos, 1995) and even to increase mortality in surgery patients (Takala et al., 1999). Further studies on both the behavior and role of IGF-1 in both TBI and SAH are needed.

5.5 Strengths of the study:

The strength of our study is that there is only one neurosurgical department in Iceland and all severe TBI, most if not all moderate TBI patients needing admittance to hospital and all SAH patients are admitted to the department. Our study, a single-center prospective study is thus a complete study on a national level that by our knowledge is novel. As we cannot exclude at this time that some patients with severe TBI and SAH have been missed to inclusion in the study we find the incidence at least not over-interpreted. The incidence found in the study could therefore be suggestive for incidence of hormonal disturbance in the acute phase of TBI and SAH in a western country with similar life style.

5.6 Limitations of the study:

An important limitation of the study is the size of the population. Iceland had at the time of the study 318.000 inhabitants and the study period was one year, explaining the small study population. Another limitation is the timing of the first blood samples. Some patients were brought to the hospital within an hour post insult and blood samples were collected shortly after while others were injured far away from the hospital causing a delay of several hours for the first blood samples to be drawn. Correlations in our study between GCS and hormone disturbances were conflicting. GCS score predicts outcome more accurately when combine with patient age and pupillary response and is better at predicting outcome when either high or low (129). GCS may not be have been the best inclusion criteria as we experienced that some patients with very low GCS recovered quickly and were discharged and did not attend to follow up and others with higher GCS had a clinical course indicating more severe injury than the GCS score indicated.

Further, the study design did not include interference of the treatment post insult, 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. Interfering with that treatment could not only be wrong but even hazardous.

6 Conclusion:

We conclude that neuroendocrine disturbances are common in both the acute phase of TBI and SAH. Patients with TBI are of greater risk for critical illness induced decrease in activity of the HP-adrenal axis in the acute phase compared to patients with SAH. Diagnosing true HP-adrenal deficiency is difficult, even today, but at the same time it is the most important hormone deficiency to identify and treat. Furthermore there is ongoing discussion about which doses of hydrocortisone to use (52).

Disturbance of the HP-gonadal axis affects the majority of male TBI and SAH patients in the acute phase. The suppression of the axis is more at the pituitary level in TBI patients compared to SAH patients and that may be explained by different causative mechanisms. Low testosterone on day 6 in SAH patients is strongly correlated to longer ICU stay indicating higher risk of suppressed HP-gonadal axis with more severely ill SAH.

The increased levels of prolactin in both TBI and SAH on admittance may indicate a risk of pituitary disturbance and therefore a need for follow up of the pituitary hormonal axis after the insult.

Even though the HP-thyroid axis is more suppressed in more severely ill TBI and SAH patients, overt disturbance in the HP-thyroid axis was uncommon in both TBI and SAH. Nevertheless, evaluation of this axis after TBI and SAH cannot be omitted

The HP-somatotroph axis is disturbed in the early acute phase of TBI and SAH. That disturbance resolves in TBI patients after the first week from the insult but remains suppressed in SAH patients. Again, the causative mechanism for the hormonal disturbance of the somatotroph axis may differ between TBI and SAH.

Our results regarding the use of following variables as predictive factor for neuroendocrine disturbance in the acute phase of TBI and SAH was inconclusive, GCS, Hunt an Hess, APACHEII, length of ICU stay, S100b, dilatation of pupil or the occurrence of ischemic events. In general when there seemed to be 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.

The clinical significance of disturbances in other than the HP-adrenal axis, whether adaptive or maladaptive is uncertain. Different causative mechanisms may explain hormonal disturbances in TBI and SAH. Clinicians should evaluate the HP-adrenal axis on indication in the acute phase of TBI and SAH as treatment with hydrocortisone may be life-saving. 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.

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