PITUITARY DYSFUNCTION AND RELATION TO COGNITIVE AND GLOBAL OUTCOME AFTER TRAUMATIC BRAIN INJURY OR SUBARACHNOID HAEMORRHAGE

Anna Tölli

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Pituitary Dysfunction and Relation to Cognitive and Global Outcome after Traumatic Brain Injury or Subarachnoid Haemorrhage

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my father Emil and my husband Jukka,
who have been the greatest supports in my life.

“Try not to become a man of success, but rather try to become a man of value.”
– Albert Einstein
ABSTRACT

Traumatic brain injury (TBI) and aneurysmal subarachnoid haemorrhage (aSAH) are leading causes of deaths and may cause permanent physical, cognitive, behavioural, and psychosocial disabilities limiting daily activities in survivors. One potential complication of TBI and aSAH is deficient secretion of one or more pituitary hormones. The prevalence of pituitary dysfunction (PiD) following TBI or aSAH varies significantly among published studies.

The aims of this thesis were to increase knowledge about PiD after TBI and aSAH and to explore the clinical impact of such dysfunction on cognitive and global outcome after TBI and aSAH. For this purpose, a cohort of 84 adult patients with moderate to severe TBI and 46 with aSAH was followed with repeated assessments of pituitary function and global and cognitive function up to 12 months post-event. Of the baseline cohort, 56 patients with TBI and 35 with aSAH were assessed at all-time points.

**Paper I** reports findings in the acute stage when hypocortisolism was seen in 12% of patients with TBI and 14% with aSAH and thyroid deficiency was seen in 17% of patients with TBI and 20% with aSAH. We found no relations between hormonal levels and injury variables and no marker of increased risk for pituitary deficiency.

**Paper II** reports findings during the first year after the event. Perturbations in pituitary function were most frequent early after the event but continued to occur until 12 months post-event. The most frequent was hypogonadotrope hypogonadism observed in 27% of patients with TBI and 41% with aSAH at 6 months, and in 21% of patients with TBI and 23% with aSAH at 12 months. Thyroid deficiency was seen in the acute stage in 24% of patients with TBI and 23% with aSAH, in 7% of patients with TBI and 3% with aSAH at 3 months, in 4% of patients with TBI and 3% with aSAH at 6 months, and in 0% of patient with TBI and 6% with aSAH at 12 months. Adrenal deficiency was seen in the acute stage in 11% of patients with TBI and 15% with aSAH, in 6% patients with TBI and 0% with aSAH at three months, in 2% patients with TBI and 3% with aSAH at six months and in 4% patients with TBI and none with aSAH at 12 months. Low levels of insulin-like growth factor 1 (IGF-I), a marker for growth hormone activity, were seen in 17% of patients with TBI and 12% with aSAH at 6 months and in 14% of patients with TBI and 3% with aSAH at 12 months. In total, 7 out of 91 patients required hormonal replacement (4 testosterone, 1 growth hormone, 2 hydrocortisone). No relations were seen between hormonal levels and injury variables.

In **Paper III** we compared the time course of cognitive and global recovery in the two diagnostic groups and explored the relations between acute injury severity markers and clinical outcome. Cognitive function was still impaired in 63% of patients with TBI and 76% with aSAH at 3 months but improved significantly between all-time points in both groups except from 6 to 12 months after TBI. The proportion of patients with cognitive impairments was not significantly different between groups at any time point. At 12 months, 62% patients with TBI and 63% with aSAH had good outcome according to the Glasgow Outcome Scale Extended (GOSE), 64% of patients with TBI and 41% with aSAH had good cognitive
function according to the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS), and 55% of patients with TBI and 40% with aSAH had good cognitive functioning according to Rancho Los Amigos Cognitive Scale-Revised (RLAS-R). Cognitive function according to BNIS correlated with cognitive/behavioural function according to the RLAS-R and with global outcome according to the GOSE. Acute Glasgow Coma Scale (GCS) scores were associated with cognitive function according to the BNIS T-scores after TBI but not after aSAH. BNIS T-scores after aSAH were not related to Hunt and Hess scores or to Fisher scores.

In Paper IV we explored associations between pituitary dysfunction and clinical outcome at 12 months after TBI and aneurysmal SAH. Controlling for baseline variables, low levels of gonadal hormones were associated with lower GOSE score (b = −0.804, p = 0.033), high levels of prolactin were associated with lower RLAS-R scores (b = −1.418, p = 0.034), and high levels of IGF-I were associated with lower RLAS-R scores (b = −1.784, p = 0.002) and lower GOSE scores (b = −1.491, p = 0.006). Thus, pituitary dysfunction during the first year after TBI and aSAH might impact on clinical outcome at 12 months.

In conclusion, these studies demonstrate that PiD occurs from the acute phase until 12 months after TBI and aSAH. The study supports the need for systematic follow-up of pituitary function after moderate or severe TBI or aSAH even though only a few patients need replacement hormonal therapy. The study could not identify a marker of increased risk for pituitary dysfunction. Cognitive improvements after aSAH and TBI showed similarities and correlate with global function. GCS scores were associated with outcome after TBI but not after aSAH. Pituitary dysfunction during the first year after TBI and aSAH might impact on clinical outcome at 12 months, and further studies are needed to fully clarify the clinical importance and optimal management of pituitary dysfunction after TBI and aSAH.
LIST OF SCIENTIFIC PAPERS


IV. Impact of pituitary dysfunction on cognitive and global outcome after Traumatic Brain Injury and aneurysmal Subarachnoid Haemorrhage. Tölli, A., Höybye, Ch., Bellander, B-M., Borg, J.

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Paper III is an original manuscript published in Brain Injury and reprinted with permission from the publisher.

Paper IV is submitted to Journal of Rehabilitation Medicine.
CONTENTS

1 Background........................................................................................................................................1
   1.1 Traumatic brain injury.....................................................................................................................1
      1.1.1 Definition, causes, and severity of traumatic brain injury .........................................................1
      1.1.2 Incidence of traumatic brain injury .............................................................................................1
      1.1.3 Early management after traumatic brain injury .........................................................................2
   1.2 Subarachnoid haemorrhage............................................................................................................3
      1.2.1 Definition, causes and severity of subarachnoid haemorrhage ..................................................3
      1.2.2 Incidence of subarachnoid haemorrhage ....................................................................................4
      1.2.3 Early management after subarachnoid haemorrhage ................................................................4
   1.3 Neurorehabilitation after traumatic brain injury and subarachnoid haemorrhage ..........................5
   1.4 Outcome after traumatic brain injury and subarachnoid haemorrhage ...........................................6
   1.5 Acquired pituitary dysfunction ........................................................................................................9
      1.5.1 Pituitary dysfunction after traumatic brain injury ........................................................................10
      1.5.2 Pituitary dysfunction after subarachnoid haemorrhage ...............................................................11
      1.5.3 Predictors for hypopituitarism after traumatic brain injury and subarachnoid haemorrhage ....12
      1.5.4 Impact of pituitary dysfunction on clinical outcome after traumatic brain injury and subarachnoid haemorrhage ...........................................................................................................12
      1.5.5 Evaluation of hypothalamic-pituitary function ..........................................................................13

2 Aims.....................................................................................................................................................15
   2.1 General aim.......................................................................................................................................15
   2.2 Specific aims......................................................................................................................................15

3 Methods ..............................................................................................................................................16
   3.1 Design and ethical approval ..............................................................................................................16
   3.2 Patient selection and data collection ...............................................................................................16
   3.3 Severity grading...............................................................................................................................16
   3.4 Radiological evaluation .................................................................................................................18
   3.5 Biomarker analysis ..........................................................................................................................18
   3.6 Pupil size and pupil light reactions ................................................................................................18
   3.7 Secondary insults ...........................................................................................................................18
   3.8 Assessment of pituitary function .....................................................................................................19
   3.9 Assessment of clinical outcome .....................................................................................................22
      3.9.1 Assessment of cognitive and affective function ...........................................................................22
      3.9.2 Activities of daily living ..............................................................................................................23
      3.9.3 Global outcome ..........................................................................................................................23
      3.9.4 Quality of life assessment .........................................................................................................24
   3.10 Statistical analysis ........................................................................................................................24

4 Results ................................................................................................................................................26
5 Discussion ..................................................................................................................45
  5.1 Pituitary dysfunction after traumatic brain injury or aneurysmal subarachnoid haemorrhage ........................................................................................................45
    5.1.1 Pituitary dysfunction in acute phase after traumatic brain injury or aneurysmal subarachnoid haemorrhage ........................................................................45
    5.1.2 Pituitary dysfunction during the first year after traumatic brain injury or aneurysmal subarachnoid haemorrhage .........................................................46
    5.1.3 Development over time ....................................................................................49
    5.1.4 Relation to traumatic brain injury or aneurysmal subarachnoid haemorrhage characteristics ......................................................................................49
  5.2 Outcome after traumatic brain injury or aneurysmal subarachnoid haemorrhage ......................................................................................................................50
    5.2.1 Change in BNIS T-scores over time .................................................................50
    5.2.2 Change in BNIS subscales over time ...............................................................50
    5.2.3 Relations between baseline characteristics and outcome variables ............50
  5.3 Impact of pituitary dysfunction on outcome after traumatic brain injury or aneurysmal subarachnoid haemorrhage .........................................................51
    5.3.1 Associations between abnormal hormone levels and outcome ..........51

6 Limitations ...................................................................................................................53
7 Conclusions ................................................................................................................54
8 Svensk sammanfattning ..............................................................................................55
9 Acknowledgements ....................................................................................................56
10 References ..................................................................................................................59
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AACC</td>
<td>Aneurysm from Anterior Cerebral Circulation</td>
</tr>
<tr>
<td>ABI</td>
<td>Acquired Brain Injury</td>
</tr>
<tr>
<td>AChA</td>
<td>Anterior Choroidal Artery</td>
</tr>
<tr>
<td>ACoA</td>
<td>Anterior Communicating Artery</td>
</tr>
<tr>
<td>ACTH</td>
<td>Adrenocorticotrophic Hormone</td>
</tr>
<tr>
<td>ADH</td>
<td>Antidiuretic Hormone</td>
</tr>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>APCC</td>
<td>Aneurysm from Posterior Cerebral Circulation</td>
</tr>
<tr>
<td>aSAH</td>
<td>Aneurysmal Subarachnoid Haemorrhage</td>
</tr>
<tr>
<td>BI</td>
<td>Barthel Index</td>
</tr>
<tr>
<td>BNIS</td>
<td>Barrow Neurological Institute Screen for Higher Cerebral Functions</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CRASH</td>
<td>Corticosteroid Randomisation after Significant Head Injury</td>
</tr>
<tr>
<td>CRH</td>
<td>Corticotropin Releasing Hormone</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
</tr>
<tr>
<td>CSW</td>
<td>Cerebral Salt Wasting Syndrome</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CTA</td>
<td>Computed Tomography Angiography</td>
</tr>
<tr>
<td>DI</td>
<td>Diabetes Insipidus</td>
</tr>
<tr>
<td>DOC</td>
<td>Disorders of Consciousness</td>
</tr>
<tr>
<td>DRS</td>
<td>Disability Rating Scale</td>
</tr>
<tr>
<td>DSA</td>
<td>Digital Subtraction Angiography</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>EuroQoL-5 Dimension Questionnaire</td>
</tr>
<tr>
<td>EUSIG</td>
<td>Edinburgh University Secondary Insult Grades</td>
</tr>
<tr>
<td>fT3</td>
<td>free Triiodothyronine</td>
</tr>
<tr>
<td>fT4</td>
<td>free Thyroxine</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle Stimulating Hormone</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
</tr>
<tr>
<td>GEE</td>
<td>Generalised Estimating Equation</td>
</tr>
<tr>
<td>GH</td>
<td>Growth Hormone</td>
</tr>
</tbody>
</table>
GHD  Growth Hormone Deficiency
GHRH  Growth Hormone Releasing Hormone
GHRH-ARG  GHRH-arginine
GnRH  Gonadotropin Releasing Hormone
GOS  Glasgow Outcome Scale
GOSE  Glasgow Outcome Scale Extended
HADS  Hospital Anxiety and Depression Scale
HADS-A  Hospital Anxiety and Depression Scale-Anxiety
HADS-D  Hospital Anxiety and Depression Scale-Depression
HP  Hypopituitarism
HPA  Hypothalamic-Pituitary-Adrenal
HPG  Hypothalamic-Pituitary-Gonadal
HPT  Hypothalamic-Pituitary-Thyroid
HS  Hypothalamic-Somatotroph
IADL  Instrumental Activities of Daily Living
ICA  Internal Carotid Artery
ICF  International Classification of Functioning, Disability and Health
ICP  Intracranial Pressure
IGF-I  Insulin-like Growth Factor I
IHA  Interior Hypophyseal Artery
IMPACT  International Mission for Prognosis and Analysis of Clinical Trial
IR  Incidence Rate
ITT  Insulin Tolerance Test
LH  Luteinizing Hormone
LIS  Locked-in Syndrome
LiSAT  Life Satisfaction Questionnaire
LOC  Loss of Consciousness
MAP  Mean Arterial Blood Pressure
MCA  Middle Cerebral Artery
MCS  Minimally Conscious State
mRS  Modified Rankin Scale
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICU</td>
<td>Neurointensive Care Unit</td>
</tr>
<tr>
<td>PCoA</td>
<td>Posterior Communicating Artery</td>
</tr>
<tr>
<td>PICA</td>
<td>Posterior Inferior Cerebellar Artery</td>
</tr>
<tr>
<td>PD</td>
<td>Pituitary Deficiency</td>
</tr>
<tr>
<td>PiD</td>
<td>Pituitary Dysfunction</td>
</tr>
<tr>
<td>PRL</td>
<td>Prolactin</td>
</tr>
<tr>
<td>PTA</td>
<td>Posttraumatic Amnesia</td>
</tr>
<tr>
<td>PTHP</td>
<td>Post-Traumatic Hypopituitarism</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>RLAS-R</td>
<td>Rancho Los Amigos Cognitive Scale-Revised</td>
</tr>
<tr>
<td>RLS</td>
<td>Reaction Level Scale</td>
</tr>
<tr>
<td>SAH</td>
<td>Subarachnoid Haemorrhage</td>
</tr>
<tr>
<td>SIADH</td>
<td>Syndrome of Inappropriate ADH Secretion</td>
</tr>
<tr>
<td>SHA</td>
<td>Superior Hypophyseal Artery</td>
</tr>
<tr>
<td>SST</td>
<td>Short Synacthen Test</td>
</tr>
<tr>
<td>T3</td>
<td>Triiodothyronine</td>
</tr>
<tr>
<td>T4</td>
<td>Thyroxine</td>
</tr>
<tr>
<td>TBI</td>
<td>Traumatic Brain Injury</td>
</tr>
<tr>
<td>TRH</td>
<td>Thyrotropin Releasing Hormone</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid Stimulating Hormone</td>
</tr>
<tr>
<td>UWS</td>
<td>Unresponsive Wakefulness Syndrome</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>VS</td>
<td>Vegetative State</td>
</tr>
</tbody>
</table>
1 BACKGROUND

1.1 TRAUMATIC BRAIN INJURY

1.1.1 Definition, causes, and severity of traumatic brain injury

Traumatic brain injury (TBI) is defined as an alteration in brain function or structure caused by the transfer of external forces, such as a direct trauma to the head, acceleration or deceleration movement of the brain without direct external trauma to the head, or forces generated from a blast or explosion [1].

Globally, the causes of TBI are road traffic accidents (62%), violence (24%), falls (8%), other unintentional injuries (4%) and war (2%) [2]. In Sweden, falls are most common (57%) followed by traffic accidents (23%) [3]. There is a current trend in western countries towards an increasing proportion of TBI in the elderly after falls [4, 5].

TBI severity is most often classified according to clinical signs at first examination by use of the Glasgow Coma Scale (GCS) [6] (Table 6), and GCS scores post-resuscitation are best correlated to outcome [7]. Points are given for eye opening, motor response, and verbal response and are summarised to give a total score of 3–15, where the lowest score of 3 corresponds to the most severe injury. The Reaction Level Scale (RLS 85) was developed in and is mainly used in Scandinavia [8], and it is considered easier to use while providing the same categorisation of injury severity as the GCS [9]. The RLS 85 is based mainly on the same information as the GCS (eye, verbal, and motor responses), but separate responses are directly weighted together in one ordinal eight-step scale. RLS scoring is in the opposite direction of the GCS, where the highest RLS score of 8 reflects the most severe injuries. Other related measures are duration of loss of consciousness (LOC) or coma [10] and duration of posttraumatic amnesia (PTA) [11]. Commonly applied cut off values for mild, moderate and severe TBI are presented in Table 1.

**Table 1:** Classification of severity of traumatic brain injury [12, 13]

<table>
<thead>
<tr>
<th></th>
<th>GCS</th>
<th>RLS 85</th>
<th>PTA</th>
<th>LOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>14–15</td>
<td>1–2</td>
<td>≤24 hours</td>
<td>0–30 min</td>
</tr>
<tr>
<td>Moderate</td>
<td>9–13</td>
<td>3</td>
<td>&gt;24 hours but &lt;7 days</td>
<td>&gt;30 min but &lt;24 h</td>
</tr>
<tr>
<td>Severe</td>
<td>3–8</td>
<td>4–8</td>
<td>≥7 days</td>
<td>≥24 hours</td>
</tr>
</tbody>
</table>

1.1.2 Incidence of traumatic brain injury

The reported annual incidence rate (IR) of TBI varies from 235 [14] to 262 [15] cases per 100,000 people in Europe to 344 per 100,000 people in Asia and 538 per 100,000 people in the US [16]. In Sweden the IR is 259 per 100,000 people [17]. IR is highest among young adults and more common in men. The reported male:female ratio is around 3:2 (in the US the IRs are 618 per 100,000 men and 399 per 100,000 women) [16]. The mortality rate of TBI varies from 15 cases per 100,000 people in Europe to 18 per 100,000 in the US and 20 per
100,000 in Asia [14]. The rates of hospitalisation and death are highest for older adults aged 75 years and older [16].

In Europe, it is estimated that 79% of TBI cases are mild, 12% are moderate, and 9% are severe respectively, in the US it is estimated that 80% are mild, 10% are moderate, and 10% are severe, and in Asia it is estimated that 78% are mild, 9% are moderate, and 13% are severe [14].

1.1.3 Early management after traumatic brain injury

Current guidelines [18, 19] for the acute management of patients with moderate to severe TBI highlight the importance of qualified care already at the site, fast transportation to hospital and neurointensive care and neurosurgery when needed.

The acute management must consider that the complex pathophysiology of TBI involves not only the primary mechanical event and subsequent initiated injury cascade [20], but also secondary insults [21, 22]. Secondary insults are defined according to the Edinburgh University Secondary Insult Grades (EUSIG) [22], and are graded as mild, moderate, or severe (Table 2). To be classified as a secondary insult, the deviation from the normal range must persist for at least 5 consecutive minutes.

Table 2: Secondary insults after brain injury [22]

<table>
<thead>
<tr>
<th>Secondary insult</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hypertension, ICP (mmHg)</td>
<td>20–30</td>
<td>30–40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Hypotension MAP (mmHg)</td>
<td>55–70</td>
<td>40–55</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Hypotension SAP (mmHg)</td>
<td>70–90</td>
<td>50–70</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Hypertension MAP (mmHg)</td>
<td>110–130</td>
<td>130–150</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Hypotension SAP (mmHg)</td>
<td>160–190</td>
<td>190–220</td>
<td>&gt;220</td>
</tr>
<tr>
<td>Pyrexia (°C)</td>
<td>38–39</td>
<td>39–40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Hypoxia SaO2 (%)</td>
<td>85–90</td>
<td>80–85</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Hypoxia PaO2 (kPa)</td>
<td>7–8</td>
<td>7–6</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Hypercarbia PaCO2 (kPa)</td>
<td>6–8</td>
<td>8–10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Hypocarbia pCO2 (kPa)</td>
<td>2.5–3</td>
<td>2–2.5</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Bradycardia (bpm)</td>
<td>40–50</td>
<td>30–40</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Tachycardia (bpm)</td>
<td>120–135</td>
<td>135–150</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Poor cerebral perfusion, CPP (mmHg)</td>
<td>50–60</td>
<td>40–50</td>
<td>&lt;40</td>
</tr>
</tbody>
</table>

ICP: intracranial pressure; MAP: mean arterial blood pressure; SAP: systolic arterial blood pressure; SaO2: oxygen saturation; PaO2: pressure of oxygen; PaCO2: pressure of carbon dioxide; bpm: beats per minute; CPP: cerebral perfusion pressure.

These secondary insults might cause hypoxic or ischemic damage to the already injured brain [21].

Other systemic complications include clinically significant hyponatremia (plasma sodium <130 mmol/L), which is seen in 15% of patients with TBI [23, 24]. Hyponatremia is usually attributed with either cerebral salt wasting syndrome (CSW) or syndrome of inappropriate
antidiuretic hormone (ADH) secretion (SIADH) [25]. The cause of CSW is still unknown. Hyponatremia in CSW is secondary to urine sodium wasting rather than volume expansion [26]. SIADH depends on uncontrolled ADH release, which leads to water retention and hyponatremia. After TBI, SIADH is more common than CSW (60–80% and 1–35%, respectively) [24, 27].

Routine diagnostics in the acute setting comprise structural imaging with computed tomography (CT) scan and structural magnetic resonance imaging. Diffusion tensor imaging might be useful in the assessment of white matter tracts [28].

A number of other markers of injury severity are also increasingly used. Damage to neurons and neuroglial cells causes a release of various proteins, some of them crossing the blood brain barrier and leaking into the peripheral circulation. Two proteins, S100B and glial fibrillar acidic protein, both marking astroglial injury, have been shown to increase in patients with TBI and to correlate with GCS scores and neuroradiological findings [29]. Neuronal specific enolase is released into cerebrospinal fluid (CSF) and serum and has been proposed as another biomarker. Other biomarkers, related to axonal damage, such as neurofilament light protein, and neuronal and glial damage such as spectrin breakdown products, are currently under investigation.

1.2 SUBARACHNOID HAEMORRHAGE

1.2.1 Definition, causes and severity of subarachnoid haemorrhage

Subarachnoid haemorrhage (SAH) is often considered a subgroup of stroke. The IR of stroke in Europe is 254 per 100,000 people [30], and in the US the rate is 373 per 100,000 people [31] and in Sweden it is 314 per 100,000 people [30]. About 2–5% of all strokes are caused by non-traumatic subarachnoid haemorrhage [32].

SAH consists of saccular aneurysm in 85% of cases, so-called non-aneurysmal perimesencephalic haemorrhage in 10% of cases, and other rare conditions in the remaining 5% of cases [33]. Saccular aneurysms arise at sites of arterial branching, usually at the base of the brain, either on the circle of Willis itself or at a nearby branching point. The most common locations of intracranial aneurysms (Figure 1) are the anterior communicating artery with approximate incidences of 30–35%, the internal carotid artery /the posterior communicating artery (30–35%), the middle cerebral artery (20%), the basilar apex (5%), the posterior inferior cerebellar artery (3%), the superior cerebellar artery (3%) and the vertebrobasilar junction (2%) [34].

The severity of SAH is often classified according to the Hunt and Hess scale [35] (Table 7). Another commonly used scale is the Fisher scale [36] (Table 8), which is used to assess the amount of blood on CT-scan and was designed to assess the risk of cerebral vasospasm.
1.2.2 Incidence of subarachnoid haemorrhage

Gender, race and geographical region have a marked influence on the incidence of SAH. Women have a 1.6 times higher risk than men [37], and black people have 2.1 times higher risk than whites [38]. The IR increases with age and peaks between the fourth and sixth decade [39], and half the patients are younger than 55 years at the time of SAH [33].

In Finland and Japan, the incidence rates are much higher than in other parts of the world. The incidence rate of SAH varies from 23 cases per 100,000 people in Japan [40] and 20 cases per 100,000 people in Finland [41] to 9 cases per 100,000 people in most European regions [37] and 2 cases per 100,000 people in Beijing, China [39]. The IR of SAH in Northern Sweden is 18 per 100 000 people, but in Southern Sweden only 10 per 100,000 people [39]. The mortality rate of SAH is about 50%, with a trend towards gradual improvement [42]. This proportion includes 10–15% of all patients with SAH who die at home or during transportation to hospital [43].

1.2.3 Early management after subarachnoid haemorrhage

The diagnosis of SAH is based on clinical presentation and most commonly by use of a non-contrast CT-scan of the head. However, CT-scan may be negative in up to 2% of patients with SAH [44]. If no blood is seen on a head CT, a next step is to perform a lumbar puncture to confirm blood in the CSF. Aneurysms are verified by computed tomography angiography (CTA) or digital subtraction angiography (DSA).

Patients are managed in neurosurgical units and, when needed, in neurointensive care units. The two main approaches to repair an aneurysm are surgical clipping and endovascular coiling [45]. In patients who survive the initial hours after the haemorrhage, three main neurological complications can threaten the patient with a ruptured intracranial aneurysm –
rebleeding, delayed brain ischemia, and hydrocephalus. Rebleeding occurs in up to 15% of patients within the first hours after SAH [46]. Other systemic complications include hyponatremia, hyperthermia, hyperglycaemia, and hypercapnia. Clinically significant hyponatremia (plasma sodium <130 mmol/L) is seen in 20% of patients with SAH [23, 24], and the aetiology is usually SIADH or CSW [21]. After subarachnoid haemorrhage, SIADH is more common than CSW (35–75% and 0–23% respectively [47, 48].

1.3 NEUROREHABILITATION AFTER TRAUMATIC BRAIN INJURY AND SUBARACHNOID HAEMORRHAGE

Patients with acquired brain injury (ABI), such as TBI or SAH, with a need for acute neurosurgery and neurointensive care need further interventions at a neurorehabilitation centre. Most TBI and SAH patients experience a wide range of different impairments depending on the type, location, and severity of their injuries [49-51]. Problems might vary from mild to severe and can cause long-term disabilities, which are often described in terms of activity limitations and restrictions of participation in daily life according to the International Classification of Functioning, Disability and Health (ICF) [52]. The ICF is the World Health Organisation framework for measuring health and disability at both individual and population levels. The ICF allows classification of a person’s functioning and disability in multiple dimensions taking into account environmental and personal factors (Figure 2). The ICF organises information in two parts; part one includes Functioning and Disability (Body Functions and Body Structures and Activities and Participation), while part two includes contextual factors (Environmental Factors and Personal Factors).

Figure 2: Components of the ICF [52]

![Diagram of ICF components](Image)

Patients with severe brain injuries might have different levels of disorders of consciousness (DOC) such as coma, vegetative state [VS or “unresponsive wakefulness syndrome “(UWS) – see below], or minimally conscious state (MCS), which must be differentiated from locked-in syndrome (LIS) [53, 54]. Consciousness has two components – arousal and awareness.
Coma is defined as the absence of arousal. When the patient opens their eyes but still is unresponsive, the patient has developed a VS, which is defined as recovery of arousal in the absence of awareness. In the MCS, the patient shows fluctuating signs of awareness. The term VS is increasingly replaced by UWS as suggested by Laureys et al [55]. Patients with a LIS are typically cognitively intact but are unable to communicate due to extensive paralysis hindering all movements, except eye movements.

One main target of early neurorehabilitation interventions is to restore the activity level. Activity refers to a task or action performed by an individual. Activity limitations are difficulties experienced by the individual in performing activities of daily living.

The rehabilitation following ABI is a complex process, which typically has to consider a variety of medical problems in the early stage while interventions that are designed to improve or restore impaired functions and the activity level increase when the medical condition has stabilised. Multi-disciplinary neurorehabilitation for patients with ABI should be managed by a specialised interdisciplinary team of health professionals. The neurorehabilitation process often comprises inpatient and outpatient programs. There is now strong evidence from both randomised controlled trials (RCT) and non-trial-based high-quality studies that early initiation of intensive rehabilitation programs (inpatient) is associated with more rapid functional gains and better outcomes and there is also evidence that outpatient programs can help to sustain gains made in the early post-acute rehabilitation [56]. There is still a need for more evidence with regard to various specialist interventions (e.g. vocational or neuro-behavioural rehabilitation) [56] even though several non-RCT studies provide consistent support for these programs [56]. Overall, there is also an urgent need for more knowledge about factors that play a key role in the recovery process and long-term outcome including pituitary dysfunction, as approached in this PhD project.

1.4 OUTCOME AFTER TRAUMATIC BRAIN INJURY AND SUBARACHNOID HAEOMORRHAGE

The mortality rate of TBI varies from 15 cases per 100,000 people in Europe to 18 per 100,000 in the US to 20 per 100,000 in Asia [14]. The mortality rate of SAH is about 50%, with a trend towards gradual improvement [57, 58]. This proportion includes the 10–15% of all patients with SAH who die at home or during transportation to hospital [43].

TBI and SAH can cause a widespread range of impairments – depending on the type, location, and severity of the injury – and associated activity limitations and restrictions on participation in social life [49, 59, 60].

Global outcome reflects the individual's ability to regain the capacity to manage daily living tasks and responsibilities. The most commonly used outcome measures in studies of TBI are The Glasgow Outcome Scale (GOS) [61] (Table 3) or The Glasgow Outcome Scale Extended (GOSE) [62] (Table 12).
Table 3: Glasgow Outcome Scale [61]

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Dead</strong></td>
</tr>
<tr>
<td></td>
<td>Mortality from any cause</td>
</tr>
<tr>
<td>2</td>
<td><strong>Vegetative state</strong></td>
</tr>
<tr>
<td></td>
<td>Unable to interact with environment, unresponsive</td>
</tr>
<tr>
<td>3</td>
<td><strong>Severe disability</strong></td>
</tr>
<tr>
<td></td>
<td>Conscious but dependent</td>
</tr>
<tr>
<td>4</td>
<td><strong>Moderate disability</strong></td>
</tr>
<tr>
<td></td>
<td>Independent but disabled</td>
</tr>
<tr>
<td>5</td>
<td><strong>Good recovery</strong></td>
</tr>
<tr>
<td></td>
<td>Return to normal occupation and social activities, might have minor residual deficits</td>
</tr>
</tbody>
</table>

The most commonly used outcome measure in studies of SAH is The modified Rankin Scale (mRS) [63], which assess the degree of independence in performing daily activities (Table 4). However, this scale might not be sensitive enough to capture clinically relevant cognitive and other disabilities, and more studies are needed within this area [49].

Table 4: The modified Rankin Scale [63]

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td><strong>No symptoms</strong></td>
</tr>
<tr>
<td>1</td>
<td><strong>No significant disability</strong></td>
</tr>
<tr>
<td></td>
<td>Able to carry out all usual activities, despite some symptoms</td>
</tr>
<tr>
<td>2</td>
<td><strong>Slight disability</strong></td>
</tr>
<tr>
<td></td>
<td>Able to look after own affairs without assistance, but unable to carry out all previous activities</td>
</tr>
<tr>
<td>3</td>
<td><strong>Moderate disability</strong></td>
</tr>
<tr>
<td></td>
<td>Requires some help, but able to walk unassisted</td>
</tr>
<tr>
<td>4</td>
<td><strong>Moderately severe disability</strong></td>
</tr>
<tr>
<td></td>
<td>Unable to attend to own bodily needs without assistance, and unable to walk unassisted</td>
</tr>
<tr>
<td>5</td>
<td><strong>Severe disability</strong></td>
</tr>
<tr>
<td></td>
<td>Requires constant nursing care and attention, bedridden, incontinent</td>
</tr>
<tr>
<td>6</td>
<td><strong>Dead</strong></td>
</tr>
</tbody>
</table>

Using the mRS, Nieuwkamp et al [64] reported that 36–55% of patients with SAH recover independence, defined as scores of 0–3, during the first year.

**Activities of Daily Living** (ADL) are basic self-care tasks that people tend to do every day without needing assistance, also called primary ADL. **Instrumental Activities of Daily Living** (IADL) refer to self-care tasks that are related to independent living and require more complex thinking skills, including organisational skills. Studies indicate that deficits in ADL are present in 4% to 12% of patients who have experienced TBI [65, 66] or aneurysmal SAH (aSAH) [67, 68].
Cognitive dysfunction is one important cause of disability after TBI and SAH [49, 60, 69] and might impact on both primary ADL and IADL, i.e. on the ability to return to work and to return to driving and on quality of life. Cognitive impairments after moderate to severe TBI and SAH may include deficits in memory, attention, executive function, language, orientation, visuospatial processing, and processing speed. Cognitive impairments after TBI and SAH improve with time, especially in the first year after event [49, 60, 69, 70], but some persisting impairments are common. Patients with moderate to severe TBI have up to 65% long-term cognitive dysfunction [59]. Dikmen et al [60] reported that in patients with severe brain injury, memory dysfunction was observed in 56%, difficulties in orientation and language in 16%, and slow information processing in 34%. One year after aSAH 46% had incomplete recovery and of them 50% had memory problems [68]. Another study showed that motor impairments recovered significantly during the 6 months post-event, while memory did not improve over the same time [71]. Al-Khindi et al [49] reported in patients with aSAH that up to 60% exhibited memory dysfunction, 75% exhibited executive dysfunction, and up to 75% exhibited language problems. Cognitive impairments tend to improve with time, especially in the first year after event, but 50% still have deficits in memory and 14% still have deficits in language 1 year after aSAH [70].

Mood disturbance are common after TBI and aSAH, and symptoms of anxiety and depression are observed in up to 50% of patients during the one and one and half years after TBI [72] and aSAH [49, 73].

Fatigue occur in up to 53% patients with TBI [74] and in up to 65% patient with aSAH [75] during the first year after the event.

Motor impairments are less prominent than cognitive or behaviour impairments after TBI and aSAH, but might contribute to long-term disability [76].

All remaining deficits after TBI and aSAH may impact social participation, life satisfaction, and quality of life (QoL) [77].

Prediction models for TBI [78], presented by the Medical Research Council (MRC) CRASH (Corticosteroid Randomisation After Significant Head Injury) Trial Collaborators [79] and by the International Mission for Prognosis and Analysis of Clinical Trial (IMPACT) study group [80], allow the prediction of mortality and unfavourable outcome based on a brain injury and other variables (Table 5).
Table 5: Comparison of CRASH and IMPACT prediction models [78]

<table>
<thead>
<tr>
<th></th>
<th>Predicted outcome</th>
<th>Core model</th>
<th>CT model</th>
<th>Laboratory model</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPACT</td>
<td>Mortality or unfavourable outcome at 6 months</td>
<td>Age, motor score, pupil reactivity</td>
<td>Core model plus: hypoxia, hypotension, CT classification, traumatic subarachnoid haemorrhage on CT, epidural mass on CT</td>
<td>Core model plus: glucose and haemoglobin concentrations</td>
</tr>
<tr>
<td>CRASH</td>
<td>Mortality at 14 days or unfavourable outcome at 6 months</td>
<td>Age, GCS score, pupil reactivity, major extracranial injury</td>
<td>Core model plus: petechial haemorrhages, obliteration of the third ventricle or basal cisterns, subarachnoid bleeding, midline shift &gt;5mm, non-evacuated hematoma</td>
<td></td>
</tr>
</tbody>
</table>

The IMPACT model is focused on moderate to severe TBI, while the CRASH model also includes mild injury. Various studies have validated these models [78, 79]. Recent reports from a longitudinal multicentre study of patients with severe TBI in Scandinavia demonstrated that prediction might be improved by use of the following “neurorehabilitation” variables: 1) patients in MSC or anaesthetized 3 weeks after injury have a better prognosis than patients in coma or UWS, which cannot be explained by the acute prognostic models [80], 2) delays in rehabilitation admission were negatively associated with outcome [81] and 3) there was a strong association between subacute complications such as epilepsy at 3 weeks, and percutaneous endoscopic gastrostomy feeding and weight loss at 3 months, and unfavourable outcome at 12 months post injury that is incompletely explained by acute injury severity [82]. Following TBI secondary insults [21], such as systemic hypotension, hypoxemia, pyrexia, increasing intracranial pressure (ICP) occurs and has been shown to be associated with poor outcome in TBI patients [22, 83, 84].

Impairments after SAH depend not only on the primary injury, but also on the development of spasm-related secondary ischemia [85-88], other secondary insults [89], critical illness neuropathy or myopathy [90, 91] and the treatment method chosen to secure the aneurysm [92, 93]. A Cochrane Review showed that endovascular coiling might be associated with better outcome when compared to surgical clipping [94]. Data from a large, longitudinal study – The Barrow Ruptured Aneurysm Trial [95] – showed no difference in outcome at 6 year follow-up between the two treatment groups, but coiling was superior for treatment of posterior circulation aneurysms.

1.5 ACQUIRED PITUITARY DYSFUNCTION

The hypothalamus plays a significant role in the endocrine system, and it links the nervous system to the endocrine system via the pituitary gland. Secretion of pituitary hormones is controlled by the release of hormone-releasing hormones, including corticotropin releasing hormone (CRH), thyrotropin releasing hormone (TRH), gonadotropin releasing hormone
(GnRH), and growth hormone releasing hormone (GHRH) and inhibiting factors (somatostatin, dopamine) from the hypothalamus [96, 97]. The pituitary gland is vascularised with branches of the internal carotid artery (ICA) called the superior hypophyseal artery (SHA) and the interior hypophyseal artery (IHA) [98]. The SHA and IHA form a portal system in the pituitary. The releasing and inhibiting hormones are secreted into the primary capillary plexus and then to the hypophyseal portal veins through which they are transported to the secondary capillary plexus in the anterior lobe of the pituitary (adenohypophysis) where they bind to receptors that activate or inhibit the release of pituitary hormones [99]. The following hormones are secreted by the anterior pituitary: thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), growth hormone (GH), follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL). The neurosecretory neurons in the hypothalamus release ADH/vasopressin and oxytocin into the general circulation in the posterior lobe of the pituitary (neurohypophysis).

1.5.1 Pituitary dysfunction after traumatic brain injury

Pathophysiology

The pathophysiology of posttraumatic hypopituitarism (PTHP) is incompletely understood, but various studies suggest that multiple factors might be involved. The primary brain injury might directly damage the pituitary, infundibulum, or hypothalamus [100], and secondary insult from hypotension, hypoxia, anaemia, and brain swelling causing restriction of flow in the long hypophyseal portal vessels might lead to an ischemic injury to the pituitary gland [100, 101]. Transient stress of critical illness is another factor behind PTHP [100]. Acute critical illness, activates the anterior pituitary function and increases circulating concentrations of ACTH, cortisol, GH, and PRL, which together with low gonadotrope hormones and low triiodothyronine syndrome are described as part of important adaptive stress responses. In prolonged critical illness, reduced secretion of anterior pituitary hormones and the so-called "wasting syndrome" occur (adrenal cortisol synthesis and secretion can be affected by cytokines, causing functional adrenal insufficiency) [102]. Other potential causes are effects of medications [103], antipituitary antibodies [104], and neuroinflammation [105].

Prevalence

The prevalence of PTHP varies significantly between studies. Several factors might affect the prevalence of PTHP including the time interval between TBI and the investigation of pituitary function (acute vs. later phases), differences in inclusion/exclusion criteria (e.g. severity of the injury), variations in testing protocols (static vs dynamic tests), confounding factors (e.g. obesity), and different levels for diagnosis of hormone deficiencies. The natural course of PTHP is still unclear, and some cases might be transient while others might be late-onset [106-111].

In 2007, Schneider et al [112] published the first systematic review of hypopituitarism (HP) after TBI and showed a prevalence of PTHP of 27.5%. They reported that the prevalence of
HP in patients with mild, moderate, and severe TBI was estimated to be 16.8%, 10.9%, and 35.5%, respectively.

The prevalence of HP in the acute phase following TBI varies significantly among studies and ranges from 53% to 76% [103, 106-109, 113-122]. The prevalence of HP in the chronic phase (12 months post-event) following TBI also varies significantly among studies and ranges from 11% to 51% [106-111, 120-128]. Based on the above studies in the acute phase after TBI, the most common deficiencies are corticotrophin, gonadotrophic, and GH deficiencies, whereas in the chronic phase the most common deficiencies are GH and gonadotrophic hormone.

In one of the latest reviews from 2014, Lauzier et al [129] showed that 31% of patients with TBI, had long-term (>12 months) HP, and the risk factors for PTHP are older age, severity of brain injury, and skull fracture. In 2015, Klose et al [130] published a new review of prevalence of PTHP and showed that prevalence was 26%, which is similar to results from the review of Schneider et al [112].

1.5.2 Pituitary dysfunction after subarachnoid haemorrhage

Pathophysiology

Few data exist regarding the pathophysiology of HP in SAH. Suggested causes can be haemorrhages in the pituitary after SAH [131] and ischemic lesions in the hypothalamopituitary system due to vasospasm [132]. One study showed regional tissue damage with reduction of cerebral blood flow in single photon emission computed tomography [133]. Another study reported that the bleeding triggers a pro-inflammatory cascade that leads to various complications of SAH [134].

Prevalence

The true prevalence of HP after SAH is still not known, and opposing results have been reported. The natural course of HP after SAH is also unclear, and some deviations might be transient while others might develop late after the event [135]. In 2007, Schneider et al [112] published the first systematic review of HP following aSAH and reported a prevalence of HP after aSAH of 47%, while an updated systematic review by Khajet et al in 2014 [136] reported a prevalence rate from 0% to 55%.

Some studies reported a prevalence of HP following SAH from 37% to 64% in the acute phase [123, 135, 137-139] and from 0% to 41% in the chronic phase [123, 135, 137, 140-142]. Based on the above studies, the most common deficiencies in the acute phase are gonadotrophic hormone, GH, and corticotrophin deficiencies, whereas in the chronic phase the most common deficiencies are GH, corticotrophin and gonadotrophic hormone.

In their very extensive review from 2015, Can et al [143] showed that pituitary deficiency (PD) after aSAH varied from 5% to 45% between 3 to 6 months after the initial bleeding (subacute phase) and from 0% to 55% after 6 months post-event (chronic phase). Multiple
pituitary deficiencies ranged from 0% to 25% in the subacute phase and from 0% to 14% in the chronic phase. GH deficiency varied from 0% to 25% in the subacute phase and from 0% to 37% in the chronic phase, adrenal insufficiency varied from 0% to 28% in the subacute phase and from 0% to 40% in the chronic phase, secondary hypothyroidism was 4% in both the subacute and chronic phases, gonadal deficiency was 11% in the subacute phase and 5% in the chronic phase, and diabetes insipidus (DI) was 5% in the subacute phase and 4% in the chronic phase. In the latest review from 2016, Robba et al [144] showed that 49% of patients with aSAH had PD in the acute phase and 26% had PD in the chronic phase, and the risk factors for PD are surgical treatment of aneurysm and younger age. Recently, Klose highlighted the risk that published studies in this area overestimate the frequency of PDs by using reference values that were not developed for the brain-injured population [145].

1.5.3 Predictors for hypopituitarism after traumatic brain injury and subarachnoid haemorrhage

It is unclear which factors predispose patients with TBI and SAH to develop HP. The severity of TBI, as assessed with GCS might be one factor for PTHP. Some studies have shown an increased risk of PTHP in patients with a lower GCS score [106, 113, 146, 147], while others have not [109, 110, 120, 148]. Other studies have reported that even mild TBI can cause HP [107, 149, 150]. Associations between diffuse brain swelling, hypoxia/hypotension, skull base fracture, increased intracerebral pressure and axonal injury and the development of HP were suggested in some studies [113, 125, 146, 147, 151], but not in others [110, 152, 153]. Other predictive markers for PTHP might be longer hospitalisation, longer intubation [147], older age [147, 151], and higher Body Mass Index (BMI) [125, 154].

The severity of SAH assessed with the Hunt and Hess scale or the severity of bleeding on CT (Fischer scale) has not been showed to be associated with HP [123, 155, 156]. In contrast, cerebral vasospasm and hydrocephalus [132], higher BMI [156] and younger age [157] have all been shown to be risk factors for HP following SAH.

1.5.4 Impact of pituitary dysfunction on clinical outcome after traumatic brain injury and subarachnoid haemorrhage

There is still little known about the impact of PD after TBI and SAH on outcome. In patients with TBI, Bondanelli et al [124] reported a negative impact of gonadotropin deficiency on cognitive/behavioural function with outcome measured with Rancho Los Amigos Cognitive Scale and with the Disability Rating Scale (DRS), and Marina et al [126] reported a negative impact on global outcome according to the GOSE. Further, Bavisetty el al [125] found that multiple pituitary deficiencies (somatotroph, gonadotroph, thyrotroph, corticotroph and posterior pituitary axis) after TBI were associated with increased disability according to the DRS and with lower quality of life, but no association with global outcome according to the GOSE. After aSAH, Kronvall et al [77] found that patients with HP (somatotroph, gonadotroph, corticotroph, thyrotroph axes) had worse outcome according to the GOS. In the study of TBI, Schneider et al [158] showed that patients with multiple pituitary hormone deficiencies (somatotroph, corticotroph axes) had worse GOS scores, but this was no longer
significant if hormones were analysed alone. Lammert et al in the study on aSAH [142] showed that patients with multiple pituitary hormone deficiencies (somatotroph, gonadotroph, thyrotrhop axes) had worse GOS scores. Some other studies on TBI [108, 159] and SAH [138] also reported worse outcome according to the GOS in patients with multiple hormone deficiencies.

Marina et al [126] reported lower GOSE scores in patients with TBI and elevated stress hormones (prolactin, IGF-I, and cortisol).

Olivecrona et al [160] found that significantly lower levels of free triiodothyronine (fT3) and TSH in the acute stage after TBI were associated with an unfavourable outcome according to the GOS at 3 months post TBI.

Although the results of several previous studies indicate that PD may have a negative impact on clinical outcome, recent reviews point out the need for more studies in this area [129, 144].

1.5.5 Evaluation of hypothalamic-pituitary function

The hypothalamic-pituitary-adrenal (HPA) axis

The adrenal gland produces cortisol after response to ACTH secretion from the anterior pituitary, which in turn is secreted after stimulation by corticotropin releasing hormone and vasopressin from the hypothalamus. HPA axis deficiency can be assessed by the early morning cortisol level, and serum cortisol <100 nmol/L strongly suggests ACTH deficiency in the context of suspected pituitary pathology. An early morning cortisol level ≥400 nmol/L is considered normal [161], and in stressful situations cortisol would be expected to be ≥500 nmol/L [162].

For further assessment, the short Synacthen test (SST, an ACTH stimulation test) is used, with administration of Synacthene (synthetic ACTH) that stimulates adrenal cortisol secretion [163]. SST is presented later. Another test is the insulin tolerance test (ITT) in which hypoglycaemia stimulates CRH activity and in turn ACTH activity and the production of cortisol. Adequate hypoglycaemia (plasma glucose <2.2 mmol/L) must be achieved for a correct interpretation [164]. Cortisol should rise to >500 nmol/L following hypoglycaemia.

The hypothalamic-pituitary-thyroid (HPT) axis

The thyroid gland produces triiodothyronine (T3) and thyroxine (T4) in response to TSH secretion from the anterior pituitary, which in turn is secreted after stimulation by TRH from the hypothalamus. In central or secondary hypothyroidism, TSH is often in the lower part of the reference range, with a low or low-normal free T4 (fT4) [164].

The hypothalamic-pituitary-gonadal (HPG) axis

The gonadal glands (ovaries in women and testicles in men) produce estradiol and testosterone after response to FSH and LH secretion from the anterior pituitary, which in turn
are secreted after stimulation by GnRH from the hypothalamus. In central or secondary hypogonadism, estradiol or testosterone are low with low or normal FSH and LH [164].

*The hypothalamic-somatotroph (HS) axis*

GH is secreted from anterior pituitary, after stimulation by GHRH from the hypothalamus, and is inhibited by somatostatin.

GH is secreted in a pulsatile way, so random samples are worthless in the diagnosis of GH deficiency [165]. Actions of GH are mediated via the insulin-like growth factor I (IGF-I), which is a hormone mainly synthesised by the liver in response to GH. IGF-I levels below the reference range might be indicative of growth hormone deficiency (GHD) [164]. An IGF-I level within the normal reference range does not exclude GHD because 30% of patients with GH deficiency have IGF-I levels within the normal reference range [166]. Dynamic tests are required to establish the diagnosis of GHD as for example the ITT, which is the golden standard. GHD is defined as a peak growth hormone response of 3 µg/l or less during ITT [167]. Because of the brain injuries in our study cohorts, we wanted to avoid hypoglycaemia and thereby ITT. Thus we used the more suitable GHRH-arginine (GHRH-ARG) stimulation test, which is presented later.

*Prolactin*

PRL deficiency is not related to clinical disorders, except in nursing mothers. In contrast to other pituitary hormones, PRL is under inhibitory control from dopamine from the hypothalamus. For evaluation of hyperprolactinemia, it is important to scrutinise the patient’s medication because a number of pharmacological substances can increase the PRL level [168]. PRL can be elevated in response to stress, and injury in the hypothalamus or in the pituitary stalk can cause increased PRL levels.

*Antidiuretic hormone*

ADH is synthesised in the hypothalamus and transported via neurons to the posterior pituitary. Release of ADH is controlled by the osmolality of extracellular fluids. ADH regulates the osmolality of the extracellular fluid and the plasma concentration of sodium through renal water resorption. ADH deficiency leads to DI, also called cranial or neurogenic diabetes insipidus. DI is present if the plasma osmolality is >300 mOsm/kg and urine osmolality remains at <100 mOsm/kg after a period of dehydration [164]. The water deprivation test (WDT) is performed by administration of desmopressin (synthetic ADH) intramuscularly. The WDT is used to differentiate cranial diabetes insipidus and nephrogenic diabetes insipidus. In cranial DI, the urine osmolality increases to >750mOsm/kg, after desmopressin injection [164].
2 AIMS

2.1 GENERAL AIM

The overall aim of this thesis was to increase our knowledge about pituitary dysfunction (PiD) after TBI or aSAH and to study the clinical impact of such dysfunctions on cognitive and global outcome after TBI and aSAH.

2.2 SPECIFIC AIMS

The specific aims were:

1. To describe the prevalence and course of pituitary function in patients with TBI or aSAH during the first year after the event and to explore the relation between pituitary function and injury variables (Paper I-II).

2. To compare the course and outcome of cognitive and global impairments by use of the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS), the Rancho Los Amigos Cognitive Scale-Revised (RLAS-R) and the GOSE during the first year after non-traumatic SAH with corresponding data from patients with moderate to severe TBI exposed to a similar neurorehabilitation and follow up program and to explore relations between baseline characteristics and outcomes (Paper III).

3. To explore the associations between PiD occurring during the first year after TBI or aSAH on cognitive and global outcome at 12 months post injury after controlling for age, gender, and acute injury variables (Paper IV).
3 METHODS

3.1 DESIGN AND ETHICAL APPROVAL

Paper I-IV
This thesis is based on a prospective, observational study performed in a clinical environment with acute phase assessment and follow up at 3, 6, and 12 months after event.

The study protocol was approved by The Regional Ethical Review Board in Stockholm (No: 2008/3:9 2008/1574-31/3).

3.2 PATIENT SELECTION AND DATA COLLECTION

Paper I-IV
Patients admitted to the Neurointensive care unit (NICU) at Karolinska University Hospital after moderate to severe TBI or aSAH were prospectively recruited for study participation from March 1, 2009, until June 30, 2012. Inclusion was not performed during holidays for logistic and administrative reasons. Inclusion required a lowest GCS score during the first day after the event of 3–13, age ≥18 years, living in the Stockholm region, and the ability to give informed consent. For patients who were unconscious or otherwise unable to give informed consent, the closest relative was asked.

In Paper I-III, results are presented separately for patients with TBI and aSAH, while in Paper IV data from both diagnostic group were combined.

Paper I-IV
Patients were included at the NICU and followed at the Department of Rehabilitation Medicine at Danderyd University Hospital, Stockholm, Sweden, at 3 months (75–105 days), 6 months (165–200 days) and 12 months (350–420 days) post injury/illness.

Demographic data (age, gender and smoking status) and clinical, laboratory, and radiological data were collected according to a preformed protocol from the NICU medical records and transferred to the study database.

3.3 SEVERITY GRADING

Paper I-IV
The clinical severity in patients with TBI or aSAH was graded according to GCS score [6] as severe injury (GCS 3–8) or moderate injury (GCS 9–13). GCS is the most used scale for assessing the level of consciousness following TBI. Points are given for eye opening (1–4), motor response (1–6), and verbal response (1–5) and summarised to given a total score of 3–15, where the lowest score of 3 indicates the most severe injury (Table 6).
Table 6: Glasgow Coma Scale [6]

<table>
<thead>
<tr>
<th>Behaviour</th>
<th>Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye opening response</td>
<td>Open spontaneously</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Open to verbal command</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Open in response to pain</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No response</td>
<td>1</td>
</tr>
<tr>
<td>Verbal response</td>
<td>Oriented to time, place, and person</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Confused speech, disoriented</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No response</td>
<td>1</td>
</tr>
<tr>
<td>Motor response</td>
<td>Obeys commands</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Localises to pain</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Flexion/withdrawal</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Abnormal flexion</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Extension</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No response</td>
<td>1</td>
</tr>
<tr>
<td>Total score</td>
<td></td>
<td>3–15</td>
</tr>
</tbody>
</table>

Clinical severity in patients with aSAH was graded according to the Hunt and Hess scale [35] (Table 7).

Table 7: Grading of clinical status according to Hunt and Hess [35]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic or minimal headache and slight nuchal rigidity</td>
</tr>
<tr>
<td>2</td>
<td>Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy</td>
</tr>
<tr>
<td>3</td>
<td>Drowsiness, confusion, or mild focal deficit</td>
</tr>
<tr>
<td>4</td>
<td>Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity, and vegetative disturbances</td>
</tr>
<tr>
<td>5</td>
<td>Deep coma, decerebrate rigidity, moribund appearance</td>
</tr>
</tbody>
</table>

The distribution of blood in the subarachnoid space seen on CT-scan was assessed according to the Fisher scale [36] (Table 8).

Table 8: Grading of blood on computed tomography according to Fisher [36]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No blood detected</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse SAH or vertical layer &lt;1 mm thick</td>
</tr>
<tr>
<td>3</td>
<td>Localised SAH clot or vertical layer ≥1 mm thick</td>
</tr>
<tr>
<td>4</td>
<td>Intracerebral or intraventricular blood with or without SAH</td>
</tr>
</tbody>
</table>
3.4 RADIOLOGICAL EVALUATION

Paper I and II

CT lesion was graded according to the CRASH model [169], including presence of one or more petechial haemorrhages (cerebral contusions), obliteration of the third ventricle or basal cisterns, subarachnoid bleeding, midline shift >5 mm, and non-evacuated haematoma (subdural/epidural). Brain oedema, basilar skull fractures and facial fractures were added to the CT model.

Aneurysms were verified by CTA or DSA. Aneurysms were divided into aneurysm from the anterior cerebral circulation (AACC) and the posterior cerebral circulation (APCC). AACC included aneurysms from anterior communicating artery (ACoA), middle cerebral artery (MCA), anterior choroidal artery AChA, internal carotid artery (ICA) and pericallosal artery. Within AACC included aneurysms from posterior communicating artery (PCoA), basilar artery, vertebral artery, posterior inferior cerebellar artery (PICA).

3.5 BIOMARKER ANALYSIS

Paper I and IV

Serum levels of S100B were obtained at admission to the NICU and every morning, as long as the patient remained unconscious. We used the highest serum levels of S100B between 12–36 hours after ictus [170]. Serum levels of S100B were analysed at the Department of Clinical Chemistry, Karolinska University Hospital, Solna, using an automatic electrochemiluminescence immunoassay (Elecsys® S100B; Roche Diagnostics, Penzberg, Germany).

In Paper IV S100B was dichotomised into following groups: normal level <0.11 µg/L, mild 0.11–0.25 µg/L, moderate 0.26–0.50 µg/L, and severe ≥0.51 µg/L.

3.6 PUPIL SIZE AND PUPIL LIGHT REACTIONS

Pupil reactivity to light at admission was categorised as normal or abnormal in Paper I and Paper IV. Pupil size at admission was categorised as normal or abnormal in Paper I.

3.7 SECONDARY INSULTS

Paper I

All patients at the NICU were monitored online using a computerised surveillance system (ICU-pilot®; µdialysis, Stockholm, Sweden). Secondary insults were defined according to the EUSIG [22]. We investigated ICP, MAP and temperature. If any the following values exceeded a duration of 5 minutes this was classified as a secondary insult: ICP >20 mm Hg, MAP <70 mm Hg and temperature >38°C. We made a simplification by summarising the total time when the value had been outside normal range for more than 5 minutes. The secondary insults were graded as mild, moderate, or severe (Table 2).
3.8 ASSESSMENT OF PITUITARY FUNCTION

Paper I, II and IV

Acute phase: 10 days

Analyses of thyroid function, including TSH, fT4, and fT3, and an ACTH stimulation test were performed 10 days post injury or at discharge from the NICU if the patient was discharged earlier.

The ACTH stimulation test was performed at the NICU by administration of 250 µg Synacthene intravenously (i.v.). Blood samples for analysis of cortisol were obtained before and 30 minutes after injection. A normal response to the SST was defined as a serum cortisol level at 30 minutes >550 nmol/L. According to the cortisol response to the SST, patients were divided into the following three subgroups: subnormal cortisol response <550 nmol/L, normal cortisol response 550–1000 nmol/L, and exaggerated cortisol response >1,000 nmol/L.

Central hypo-thyroidism was defined as an fT4 level below the normal reference range concomitant with normal or low TSH. The reference ranges for TSH, fT4, and fT3 are given in Table 9.

Follow up: 3, 6 and 12 months

At the follow up at 3, 6, and 12 months at the Department of Rehabilitation Medicine at Danderyd University Hospital, blood was sampled between 8 a.m. and 10 a.m. A flowchart of the blood sampling is presented in Figure 3.

Figure 3: Flowchart of blood samples
At 3, 6 and 12 months, blood was analysed for thyroid function (TSH, fT4, and fT3) and cortisol. At 6 and 12 months, additional analyses were performed for IGF-I, PRL, estradiol in women, FSH in women, LH in women, and testosterone in men.

Aa SST was performed if the morning cortisol level was <400 nmol/L. A baseline cortisol level ≥400 nmol/L was defined as normal. Baseline cortisol was evaluated according to clinical status in combination with results from the literature [148, 171, 172]. According to the cortisol response in the SST, patients were divided into the same subgroups as previously described.

Decreased secretion of GH was presumed if S-IGF-I < −2SD. The GHRH-ARG stimulation test was performed if IGF-I < −2SD, but because IGF-I is a non-specific marker for GH deficiency, sustained low IGF-I at 12 months resulted in dynamic testing. An age-dependent reference range (geometrical mean ± 2 SD) for IGF-I independent of gender was calculated based on the equation for the regression line in all patients: 10log [IGF-I (µg/L)] = 2.581 − 0.00693 × age (years), with SD = 0.120 [173]. The GHRH-ARG stimulation test was performed by administration of a bolus injection of GHRH 1-29 1 µg/kg (maximum 100 µg) i.v. at 0 min followed by infusion of arginine hydrochloride 0.5 g/kg (maximum 30 g) i.v. from 0 to +30 min, and blood samples for analysis of GH were taken every 15 min from −15 to +120 min. GH deficiency was presumed if GHmax was below 11.5 µg/l for BMI <25, 8.5 µg/l for BMI 25–30, and 4.2 µg/l for BMI >30 [174].

Dynamic hormone testing was performed at the Department of Endocrinology, Karolinska University Hospital.

Thyroidal dysfunction was defined as an fT4 level below the normal reference range. Gonadotropin dysfunction in post-menopausal women was defined as FSH and either LH or estradiol below the normal reference range, and in pre-menopausal women this was in combination with amenorrhea or oligomenorrhea. Gonadotropin dysfunction in men was defined as testosterone below the normal reference range.

In Paper I-II, P-sodium (P-Na) and lowest and highest serum osmolality values were measured during the time at the NICU. In Paper II, P-Na was measured at 3, 6, and 12 months post TBI and aSAH, but serum osmolality was measured if P-Na level was below or above the normal reference range.

The reference range for TSH, fT4, fT3, cortisol, IGF-I, estradiol, FSH, LH, testosterone, prolactin, P-Na, and serum osmolality are presented in Table 9. Analyses of blood samples were performed in the Department of Clinical Chemistry of Karolinska University Hospital using routine commercial kits, and reference data were provided by the department. A few analyses during follow up were done in others departments of clinical chemistry; however, in Paper II calculations were based on reference levels.

In Paper II patients were divided into two groups – one group that showed hormonal disturbances at the first or last tests, and one group that did not show hormonal disturbances.
The first tests were performed at 10 days (cortisol and thyroid hormones) or 6 months (IGF-I, gonadotropin, and PRL). The last tests were performed at 12 months for all hormones.

In Paper IV patients were divided in groups of those, who showed hormonal disturbance at any of the tests, and those who did not show any such disturbance.

Table 9: Reference values for basal concentrations

<table>
<thead>
<tr>
<th>Blood samples</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>0.4–3.5 mU/L (DxI)</td>
</tr>
<tr>
<td>fT4</td>
<td>8–14 pmol/L (DxI)</td>
</tr>
<tr>
<td>fT3</td>
<td>3.5–5.4 pmol/L (DxI)</td>
</tr>
<tr>
<td>Cortisol (Synacthen test)</td>
<td>≥400 nmol/L normal function</td>
</tr>
<tr>
<td>Estradiol</td>
<td>&lt; 600 pmol/L for follicular phase women</td>
</tr>
<tr>
<td></td>
<td>200–2000 pmol/L for mid-cycle phase women</td>
</tr>
<tr>
<td></td>
<td>300–1000 pmol/L for luteal phase women</td>
</tr>
<tr>
<td></td>
<td>&lt;150 pmol/L for postmenopausal women</td>
</tr>
<tr>
<td>FSH</td>
<td>2.5–10.0 U/L for follicular phase women</td>
</tr>
<tr>
<td></td>
<td>4.0–14.0 U/L for mid-cycle phase women</td>
</tr>
<tr>
<td></td>
<td>0.7–8.5 U/L for luteal phase women</td>
</tr>
<tr>
<td></td>
<td>0.7–8.5 U/L for postmenopausal women</td>
</tr>
<tr>
<td>LH</td>
<td>1.8–12 U/L for follicular phase women</td>
</tr>
<tr>
<td></td>
<td>18–90 U/L for mid-cycle phase women</td>
</tr>
<tr>
<td></td>
<td>0.6–15 U/L for luteal phase women</td>
</tr>
<tr>
<td></td>
<td>18–78 U/L for postmenopausal women</td>
</tr>
<tr>
<td>Testosterone</td>
<td>10–30 nmol/L for men</td>
</tr>
<tr>
<td>Prolactin</td>
<td>3–27 µg/L for age &lt;50 years women</td>
</tr>
<tr>
<td></td>
<td>3–20 µg/L for age &gt;50 years women</td>
</tr>
<tr>
<td></td>
<td>3–13 µg/L for men</td>
</tr>
<tr>
<td>IGF-I</td>
<td>250–610 µg/L for ages 18–19 years men</td>
</tr>
<tr>
<td></td>
<td>210–600 µg/L for ages 18–19 years women</td>
</tr>
<tr>
<td></td>
<td>250–590 µg/L for ages 19–20 years men</td>
</tr>
<tr>
<td></td>
<td>220–550 µg/L for ages 19–20 years women</td>
</tr>
<tr>
<td></td>
<td>160–420 µg/L for ages 20–25 years</td>
</tr>
<tr>
<td></td>
<td>150–390 µg/L for ages 25–30 years</td>
</tr>
<tr>
<td></td>
<td>140–370 µg/L for ages 30–35 years</td>
</tr>
<tr>
<td></td>
<td>130–340 µg/L for ages 35–40 years</td>
</tr>
<tr>
<td></td>
<td>120–320 µg/L for ages 40–45 years</td>
</tr>
<tr>
<td></td>
<td>110–300 µg/L for ages 45–50 years</td>
</tr>
<tr>
<td></td>
<td>110–270 µg/L for ages 50–55 years</td>
</tr>
<tr>
<td></td>
<td>100–260 µg/L for ages 55–60 years</td>
</tr>
<tr>
<td></td>
<td>90–240 µg/L for ages 60–65 years</td>
</tr>
<tr>
<td></td>
<td>85–220 µg/L for ages &gt;65 years</td>
</tr>
<tr>
<td>P-Sodium</td>
<td>137–145 mmol/L</td>
</tr>
<tr>
<td>S-osmolality</td>
<td>280–300 mOsmol/kg</td>
</tr>
</tbody>
</table>

S-serum; P-plasma; U-unit
3.9 ASSESSMENT OF CLINICAL OUTCOME

3.9.1 Assessment of cognitive and affective function

Paper III-IV

The BNIS [175] was used to screen cognitive disturbances. A pre-screen test with scoring of three items (level of arousal 3 points, basic communication 3 points, and cooperation 3 points) is performed to judge if the person is testable. The patient must score at least two points on each of these items to be qualified for further examination with seven subscales for speech and language function (15 points), orientation (3 points), attention/concentration (3 points), visual and visuospatial problem solving (8 points), memory (7 points), affect (4 points) and awareness of own performance (1 point). The total score on the BNIS is a maximum of 50 points including the results from the pre-screen score (9 points) and 7 subscale scores (41 points). Total BNIS raw scores are converted to age-corrected standard T-points, and higher scores indicate better function. Brain dysfunction was defined as a cut-off score < 47 points for patients < 60 years, < 46 points for patients 60–69 years and < 44 points for patients > 70 years [176-178]. The BNIS has good sensitivity (92%) and acceptable specificity (56%) for brain dysfunction [179]. In a Swedish study, the sensitivity was 88% and the specificity was 78% [178]. The BNIS has been used in several studies of TBI [178, 180, 181] and stroke [178, 182, 183]. The cut-off for cognitive dysfunction for T-points was set at < 40 (i.e. < –1SD) [184]. BNIS T-points are interpreted as follows: extremely low, T-points < 30; borderline, T-points 30–39; average, T-points 40–60; superior, T-points > 60 [184].

The RLAS-R [185] was used to estimate the level of cognitive and behavioural function. The RLAS-R is a clinical scale with scores from 1 to 10 (Table 10) describing 10 phases of recovery after brain injury [186]. The lowest level is “No response, total assistance,” and the highest level is “Purposeful, appropriate: modified independent.” In Paper III, the RLAS-R levels were dichotomised into “inferior functioning” (RLAS-R score 1–8) and “superior functioning” (RLAS-R score 9–10).

Table 10: Rancho Los Amigos Cognitive Scale-Revised [185]

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No response: total assistance</td>
</tr>
<tr>
<td>2</td>
<td>Generalised response: total assistance</td>
</tr>
<tr>
<td>3</td>
<td>Localised response: total assistance</td>
</tr>
<tr>
<td>4</td>
<td>Confused/agitated: maximal assistance</td>
</tr>
<tr>
<td>5</td>
<td>Confused, inappropriate, non-agitated: maximal assistance</td>
</tr>
<tr>
<td>6</td>
<td>Confused, appropriate: moderate assistance</td>
</tr>
<tr>
<td>7</td>
<td>Automatic, appropriate: minimal assistance for routine daily living skills</td>
</tr>
<tr>
<td>8</td>
<td>Purposeful, appropriate: stand–by assistance</td>
</tr>
<tr>
<td>9</td>
<td>Purposeful, appropriate: stand–by assistance on request</td>
</tr>
<tr>
<td>10</td>
<td>Purposeful, appropriate: modified independent</td>
</tr>
</tbody>
</table>
Paper III

The Hospital Anxiety and Depression Scale (HADS) [187] was used to screen for depression and anxiety. It is divided into an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D). It consists of 14 items (7 items for HADS-A and 7 items for HADS-D) that are assessed on a 4–point scale (0–3). The total score is the sum of each subscale (0–21). Severity was classified as normal (0–7), mild (8–10), moderate (11–14) or severe (15–21) in both subscales [188]. The sensitivity and specificity of HADS is in the range of 70–90% in assessing severity of anxiety and depression in different population [189].

3.9.2 Activities of daily living

Paper III

The Barthel Index (BI) was used to assess performance in ADL [190]. The BI scale enables evaluation of functional independence in 10 activities and gives a total score of 0 to 100 (Table 11). The BI was dichotomised into “dependence” (BI 0–95) and “independence” (BI 96–100).

Table 11: Original scoring for the Barthel Index [190]

<table>
<thead>
<tr>
<th>Items</th>
<th>Unable to perform task</th>
<th>Needs assistance</th>
<th>Fully independent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding</td>
<td>0</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Chair/bed transfers</td>
<td>0</td>
<td>5–10</td>
<td>15</td>
</tr>
<tr>
<td>Grooming</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Toilet use</td>
<td>0</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Bathing</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Walking</td>
<td>0</td>
<td>5–10</td>
<td>15</td>
</tr>
<tr>
<td>Wheelchair*</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Stairs climbing</td>
<td>0</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Dressing</td>
<td>0</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Bowel control</td>
<td>0</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Bladder control</td>
<td>0</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Range</td>
<td>0</td>
<td>0–100</td>
<td>0</td>
</tr>
</tbody>
</table>

*Score only if unable to walk

3.9.3 Global outcome

Paper III-IV

The GOSE was used to assess global outcome and independence [61, 191]. The GOSE is a clinical scale with scores from 1 to 8 (Table 12) and shows good inter-rate reliability and validity after conducting the standardised interview [62, 192]. In Paper III, the GOSE scores were dichotomised into “unfavourable” outcome (GOSE 1–4) and “favourable” outcome (GOSE 5–8).
Table 12: Glasgow Outcome Scale Extended [62]

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dead</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Vegetative state</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Severe disability lower</td>
<td>Dependent on others for activities of daily living</td>
</tr>
<tr>
<td>4</td>
<td>Severe disability upper</td>
<td>Dependent on others for some activities</td>
</tr>
<tr>
<td>5</td>
<td>Moderate disability lower</td>
<td>Unable to return to work or participate in social activities</td>
</tr>
<tr>
<td>6</td>
<td>Moderate disability upper</td>
<td>Return to work at reduced capacity, reduced participation in social activities</td>
</tr>
<tr>
<td>7</td>
<td>Good recovery lower</td>
<td>Minor social or mental deficits which do not impair normal functioning</td>
</tr>
<tr>
<td>8</td>
<td>Good recovery upper</td>
<td>Full recovery, no residual complaints or deficits</td>
</tr>
</tbody>
</table>

3.9.4 Quality of life assessment

Paper III

QoL was assessed with the EuroQoL-5 Dimension Questionnaire (EQ-5D) [193]. The EQ-5D index estimates health in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and each dimension is scored as one of three levels: having no problems (1), having some or moderate problems (2), or being unable to do/having extreme problems (3). The five dimensions together with three levels allow for 243 variations of unique health states and are revised into an index with a range from −0.594 to 1, with 1.00 indicating full health. The EQ-5D also includes a visual analogue scale (VAS) ranging from 0 to 100.

Satisfaction with life was assessed with the 11-item Life Satisfaction Questionnaire (LiSat-11) [194, 195]. The LiSat-11 assesses global satisfaction with life as a whole as well as for 10 specific domains. Each question is scored on six response levels, from very satisfied (6) to very dissatisfied (1). Item scores were dichotomised into unsatisfied (1–4) and satisfied (5–6) to report results on item level.

3.10 STATISTICAL ANALYSIS

Paper I-IV

Statistical analyses were performed using IBM SPSS version 22 (Paper I-III) and version 25 (Paper IV) (IBM Corporation, Armonk, New York, USA).
We report descriptive data with central measures (mean, median or percent) and measures of spread (SD, percentile, min–max, 95% Confidence Interval (CI)).

Nonparametric methods were used because the data were not normally distributed according to the Shapiro–Wilk test of normality. The Mann–Whitney U-test was used for non-response analysis with respect to the following variables: age, BMI, GCS score, Hunt and Hess grade, Fisher grade, and peak in serum level of S-100B. The Pearson chi-squared test or Fisher’s exact test was used for non-response analysis with respect to gender.

The Mann–Whitney U-test was used to compare GCS score, Hunt and Hess grade, Fisher grade, and peak in serum level of S-100B in patients with evidence of pituitary dysfunction versus those with normal pituitary function. Fisher’s exact test was used for similar comparisons of following parameters: CT-scan findings, pupil size, and pupil reactivity to light. ANOVA was used for group comparisons of age and BMI.

The Wilcoxon signed ranks test was used for analysis of BNIS T-score, RLAS-R level, EQ-5D index, EQ-5D VAS, BI, HADS-D and HADS-A score over time (Paper III). Friedman’s test was used for comparisons of LiSat-11 score (Paper III), and the Z-test was used for analyses of population proportions (Paper III).

The generalised estimating equation (GEE) was used to explore the effect of time on cognitive function according to BNIS T-score (Paper III). The Spearman correlation coefficient was used for the analysis of bivariate correlation between BNIS T-score and GCS score, Hunt and Hess grade, Fisher grade, gender, age, GOSE score, RLAS-R level, HADS-D and HADS-A score, BI, and LiSat-11 score, and between GCS score and Hunt and Hess grade (Paper III).

The Mann–Whitney U-test was used for comparisons of the results of BNIS T-score, RLAS-R level, and GOSE score between the two subgroups of hormone dysfunction (Paper IV). The Pearson chi-square test was used for group comparisons of injury severity groups, age groups, and anterior pituitary dysfunction (Paper IV). The Kruskal–Wallis test was used for multiple comparisons of results of BNIS T-score, RLAS-R level, and GOSE score between the three subgroups of hormone dysfunction (Paper IV). The Spearman correlation coefficient was used for analysis of bivariate correlation between hormone dysfunction and BNIS T-score (Paper IV). Multiple linear regression analyses were used to examine the relationship between BNIS T-score or RLAS-R level or GOSE score and hormone dysfunctions, GCS score, gender, and age (Paper IV).

In all cases, the significance level was set at p < 0.05.
4 RESULTS

4.1 PAPER I

4.1.1 Study population

We included 130 patients, 84 with TBI and 46 with aSAH. Also included in this study were two 16–year–old patients with TBI and one patient with SAH without aneurysm.

Of the 84 patients with TBI, 65 (77%) were men and 19 (23%) were women, with a mean age of 48.3 ± 16.9 years. Of these, 63 (75%) patients had severe brain injury and 21 (25%) patients had moderate brain injury according to the admission GCS score (mean 6.6 ± 3.1 (3–13), median 7, Q1–Q3 (4–8.75)]. TBI was caused by traffic accidents (n = 29), falls (n = 47), violence (n = 5), or other (n = 3). CT-scan demonstrated petechial haemorrhages (n = 65), obliteration of the 3rd ventricle or basal cisterns (n = 24), traumatic SAH (n = 64), midline shift > 5mm (n = 31), subdural/epidural haematoma (n = 72), brain oedema (n = 16), basilar skull fractures (n = 41), and facial fractures (n = 27).

Of the 46 patients with aSAH, 38 were women and 8 were men, with a mean age of 58.3 ± 10.5 years. Of these, 31 patients had severe brain injury and 15 had moderate brain injury according to the admission GCS score (mean 7.4 ± 3.9 (3–13), median 6, Q1–Q3 (3.75–13)]. Hunt & Hess scores at admission were: 1 (n = 1), 2 (n = 3), 3 (n = 16), 4 (n = 21), and 5 (n = 5). SAH was visible on CT-scan in all patients and Fisher grades were 1 (n = 0), 2 (n = 3), 3 (n = 10), and 4 (n = 33). Out of 45 SAH patients, 34 patients had aneurysm in the anterior cerebral circulation (ACoA (n = 16), MCA (n = 12), AChA (n = 2), ICA (n = 3), pericallosal artery (n = 1)), 9 had aneurysms in the posterior cerebral circulation (PCoA (n = 4), basilar artery (n = 2), vertebral artery (n = 1), and PICA (n = 2)), and 2 had aneurysms in the anterior and posterior cerebral circulation (MCA + vertebral artery (n = 1), and MCA + PCoA (n = 1)).

4.1.2 Pituitary dysfunction in the acute stage after traumatic brain injury or aneurysmal subarachnoid haemorrhage

Hypothalamus–Pituitary–Adrenal (HPA) axis

We performed the SST in 77 patients with TBI and 43 with aSAH. Cortisol response was < 550 nmol/L in 9 (12%) patients with TBI and 6 (14%) with SAH (Figure 4). In patients with subnormal response, 7 with TBI and all 6 with aSAH had been treated with different types of steroids (methylprednisolone was used in the treatment of high ICP, hydrocortisone was used for pharyngeal swelling, and betamethasone was used in a few patients with aSAH in the treatment of brain oedema).

An exaggerated cortisol response ≥1000 nmol/L was seen in 27 (35%) patients with TBI (one patient with TBI had 3,300 nmol/L) and in 23 (53%) patients with aSAH. The proportion of patients with TBI and aSAH with subnormal, normal, and exaggerated responses to the ACTH stimulation test is presented in Figure 4.
Figure 4: Proportion of patients with TBI and aSAH with different response to the Synacthene test.

A subnormal response to the SST in patients with TBI was related to oedema on CT-scan \( (p = 0.026) \), while exaggerated response to the SST in patients with aSAH was related to a higher peak in serum level of S-100B \( (p = 0.043) \). There were no differences between cortisol response with regard to other acute injury variables in either group.

_Hypothalamus–Pituitary–Thyroid (HPT) axis_

In 14 (17%) patients with TBI and 9 (20%) with aSAH, low fT4 in combination with normal or low TSH (1 patient with TBI and 3 with aSAH) were observed (Figure 5). Thyroid deficiency was related to traumatic SAH on CT-scan in patients with TBI \( (p = 0.027) \) but not to other acute injury variables in either group.

We also observed high T4 in 8 (10%) patients with TBI and in 7 (16%) with aSAH and low fT3 in 26 (32%) patients with TBI and 19 (42%) with aSAH.

_Multiple pituitary deficiencies._

Of 9 patients with TBI and adrenal dysfunction, 5 also had thyroidal dysfunction, and among 6 patients with aSAH and adrenal dysfunction, 3 also had thyroidal dysfunction (Figure 4).

Of 27 patients with TBI and an exaggerated cortisol response to the SST, 1 also had a thyroidal dysfunction, and among 23 patients with aSAH and an exaggerated cortisol response to the SST test, 3 also had thyroidal dysfunction.
In the NICU period, high P-Na > 146 in combination with high S-osmolality > 300 mOsm/kg was noted in 63 (75%) patients with TBI and 40 (90%) with aSAH. Of these, 9 patients with TBI and 9 with aSAH had been treated with fludrocortisone, and 7 patients with TBI and 10 with aSAH had been treated with desmopressin. High plasma levels of P-Na and S-osmolality were not related to any acute injury variables in either group.

Low P-Na in combination with low S-osmolality was observed in 19 (12%) patients with TBI and 2 (4%) with aSAH. No clear distinction between CSW and SIADH could be made. Of these, 6 patients with TBI lost weight (–7.3 to –1.1 kg) and 4 increased in weight (+1.5 to +7.1 kg), while all patients with aSAH lost in weight (–6.1 to –1.4 kg).

4.1.3 Secondary insults

For patients with TBI, the total monitored time possible for analyses of ICP was 243 ± 183 h (total time 19,909.37 h), for temperature 356 ± 232 h (total time 29,880.96 h), and for MAP was 362 ± 235 h (total time 30,428.90 h). For two patients with TBI, monitoring with the ICU pilot system could not be done. The most prominent secondary insult for patients with TBI was mild pyrexia (temperature, 37–38°C) with a total time of 6,459.2 h followed by mild hypotension (MAP, <70 mm Hg) with a total time of 5357.1 h and mild intracranial hypertension (ICP, 20–30 mm Hg) with a total time of 1,166.5 h. For patients with aSAH, the total monitored time possible for analyses of ICP was 349 ± 202 h (total time 16,049.75 h), for temperature 432 ± 273 h (a total time 19,875.27 h) and for MAP was 438 ± 273 h (total time 20,129.39 h). The most prominent secondary insult for patients with aSAH was mild pyrexia with a total time of 3897.1 h followed by mild hypotension with a total time of 2,990.3 h and mild intracranial hypertension with a total time of 464.4 h.
4.2  PAPER II

4.2.1  Study population

We included 127 patients, 82 with TBI and 45 with aSAH. During the follow-up, 26 patients with TBI and 10 with aSAH dropped out for the following reasons: death (10 patients with TBI and 4 with aSAH), declined further participation in the study (12 patients with TBI and 5 with aSAH), or moved abroad (4 patients with TBI and 1 with aSAH).

Non–response analysis

For patients with aSAH or TBI who dropped out, there was no significant difference in age (p = 0.094 and p = 0.280, respectively), gender (p = 0.121 and p=0.095, respectively), or GSC (p = 0.073 and p = 0.205, respectively). A flowchart of the patients with aSAH and TBI are presented in Figure 6.

Figure 6: Flowchart of the study participants

Of the baseline cohort, 56 patients with TBI and 35 with aSAH participated in the entire study. Out of 56 patients with TBI, 41 were men and 15 were women with a mean age of 47.1 ± 16.6 years, and 12 patients had moderate brain injury and 44 patients had severe brain injury according to the admission GCS score (median 6, Q1–Q3 (4–8)]. Data are shown in Table 13.

Of the 35 patients with aSAH, 8 were men and 27 women, with a mean age of 57.4 ± 9.9 years, and 13 patients had moderate brain injury and 22 patients had severe brain injury according to the admission GCS score (median 7, Q1–Q3 (3–13)]. All patients with aSAH were in Hunt & Hess grade I–V. Haemorrhage was visible on CT-scan (Fisher grade 2–4) in all cases. Data are shown in Table 13.
Table 13: Baseline data of patients with traumatic brain injury and aneurysmal subarachnoid haemorrhage

<table>
<thead>
<tr>
<th></th>
<th>TBI (n = 56)</th>
<th>aSAH (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± S.D. (min–max)</td>
<td>mean ± S.D. (min–max)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>47.1 ± 16.6 (19–79)</td>
<td>57.4 ± 9.9 (28–76)</td>
</tr>
<tr>
<td><strong>Body Mass Index (kg/m²)</strong></td>
<td>25.6 ± 4.8 (18.5–42.2)</td>
<td>25.7 ± 4.3 (20.3–36.5)</td>
</tr>
<tr>
<td><strong>GCS</strong></td>
<td>6.3 ± 2.9 (3–13)</td>
<td>7.9 ± 4.2 (3–13)</td>
</tr>
<tr>
<td><strong>Age groups:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–59</td>
<td>40 (71.4)</td>
<td>19 (54.3)</td>
</tr>
<tr>
<td>60–69</td>
<td>13 (23.2)</td>
<td>15 (42.9)</td>
</tr>
<tr>
<td>70–87</td>
<td>3 (5.4)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td><strong>Education:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 years</td>
<td>8 (14.8)</td>
<td>11 (31.4)</td>
</tr>
<tr>
<td>=12 years</td>
<td>23 (42.6)</td>
<td>10 (28.6)</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>23 (42.6)</td>
<td>14 (40.0)</td>
</tr>
<tr>
<td><strong>Gender:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>41 (73.2%)</td>
<td>8 (22.9%)</td>
</tr>
<tr>
<td>Women</td>
<td>15 (26.8%)</td>
<td>27 (77.1%)</td>
</tr>
<tr>
<td><strong>GCS: Moderate (9–13)</strong></td>
<td>12 (21.4%)</td>
<td>13 (37.1%)</td>
</tr>
<tr>
<td><strong>Severe (3–8)</strong></td>
<td>44 (78.6%)</td>
<td>22 (62.9%)</td>
</tr>
<tr>
<td><strong>Hunt &amp; Hess grade:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3 (8.6%)</td>
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<tr>
<td>3</td>
<td>14 (40.0%)</td>
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<tr>
<td>4</td>
<td>15 (42.9%)</td>
<td></td>
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<tr>
<td>5</td>
<td>2 (5.7%)</td>
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<tr>
<td><strong>Fisher grade:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3 (8.6%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8 (22.9%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>24 (68.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Trauma cause:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traffic accident</td>
<td>25 (44.6%)</td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>28 (50%)</td>
<td></td>
</tr>
<tr>
<td>Violence</td>
<td>2 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>CT scan</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral contusions</td>
<td>45 (80.8%)</td>
<td></td>
</tr>
<tr>
<td>Obliteration of the third ventricle or basal cisterns</td>
<td>15 (26.8%)</td>
<td></td>
</tr>
<tr>
<td>Subarachnoid bleeding</td>
<td>45 (80.4%)</td>
<td></td>
</tr>
<tr>
<td>Midline shift &gt;5mm</td>
<td>21 (37.5%)</td>
<td></td>
</tr>
<tr>
<td>Subdural/epidural haematoma</td>
<td>48 (85.7%)</td>
<td></td>
</tr>
<tr>
<td>Brain oedema</td>
<td>12 (21.4%)</td>
<td></td>
</tr>
<tr>
<td>Basilar skull fracture</td>
<td>26 (46.4%)</td>
<td></td>
</tr>
<tr>
<td>Facial fracture</td>
<td>17 (30.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Aneurysm localisation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cerebral circulation (AACA)</td>
<td>15 (42.9%)</td>
<td></td>
</tr>
<tr>
<td>Anterior communicating artery (ACoA)</td>
<td>15 (42.9%)</td>
<td></td>
</tr>
<tr>
<td>Middle cerebral artery (MCA)</td>
<td>8 (22.9%)</td>
<td></td>
</tr>
<tr>
<td>Anterior choroidal artery (AChA)</td>
<td>1 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery (ICA)</td>
<td>3 (8.6%)</td>
<td></td>
</tr>
<tr>
<td>Pericallosal artery</td>
<td>1 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>Posterior cerebral circulation (APCC)</td>
<td>3 (8.6%)</td>
<td></td>
</tr>
<tr>
<td>Posterior communicating artery (PCoA)</td>
<td>3 (8.6%)</td>
<td></td>
</tr>
<tr>
<td>Basilar artery</td>
<td>1 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>1 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>Posterior inferior cerebellar artery (PICA)</td>
<td>1 (2.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>AACA + APCC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA+ PICA</td>
<td>1 (2.9%)</td>
<td></td>
</tr>
</tbody>
</table>
4.2.2 Pituitary dysfunction during the first year after traumatic brain injury or aneurysmal subarachnoid haemorrhage

**Hypothalamic-Pituitary-Adrenal axis**

Dynamic testing resulted in a cortisol concentration <550 nmol/L in 6/53 (11%) patients with TBI and 5/34 (15%) with aSAH in the acute stage, in 3/47 (6%) patients with TBI and 0/32 (0%) with aSAH at follow-up after 3 months, in 1/49 (2%) patients with TBI and 1/30 (3%) with aSAH after 6 months, and in 2/45 (4%) patients with TBI and 0/31 (0%) with aSAH after 12 months (Figure 7). In the acute stage, 5 patients with TBI and all 5 patients with a SAH had been treated with different types of steroids before the SST. Replacement therapy was clinically indicated in 2 patients with TBI and cortisol insufficiency after 12 months of follow-up.

Dynamic testing resulted in cortisol concentration >1000 nmol/L in 18 (53%) patients with TBI and 19 (56%) with a SAH in the acute stage, but at follow-up after 3, 6, and 12 months none of the patients had an exaggerated cortisol response.

**Hypothalamic-Pituitary-Thyroid axis**

Baseline testing showed low levels of fT4 in 13/55 (24%) patients with TBI (3 with low TSH) and 8/35 (23%) with aSAH (1 with low TSH) in the acute stage, in 4/54 (7%) patients with TBI (4 with low TSH) and 1/35 (3%) with aSAH (1 with low TSH) at follow-up after 3 months, in 2/52 (4%) patients with TBI (none with low TSH) and 1/34 (3%) with aSAH (none with low TSH) after 6 months, and in 0/52 (0%) patients with TBI and 2/35 (6%) with aSAH (none with low TSH) after 12 months (Figure 7). Replacement therapy was not clinically indicated in any patient.

Baseline testing also showed high levels of fT4 in 3 (6%) patients with TBI and 6 (17%) with aSAH in the acute stage, in 4 (7%) patients with TBI and 4 (11%) with aSAH at follow-up after 3 months, after 6 months in 2 (4%) patients with TBI and 2 (6%) with aSAH after 6 months, and in 4 (8%) patients with TBI and 1 (3%) with aSAH after 12 months.

**Hypothalamic-Somatotroph (HS) axis**

Low concentrations of IGF-I (< –2SD) indicating GHD were seen in 2/52 (4%) patients with TBI and 3/34 (9%) with aSAH after 6 months, and in 6/52 (12%) patients with TBI and 2/35 (6%) with aSAH after 12 months (Figure 7). Dynamic assessment at follow-up after 12 months using the GHRH-ARG stimulation test was only performed in 4 patients with TBI (and no patient with aSAH), and showed one response indicating GHD (2%). Only one patient with TBI received replacement with growth hormone after 12 months.

At follow-up after 6 months, testing also showed a high level of IGF-I (>2SD) in 9 (17%) patients with TBI and in 4 (12%) with aSAH. After 12 months, 7 (14%) patients with TBI and 1 (3%) with aSAH presented with high levels of IGF-I.
Hypothalamic-Pituitary-Gonadal (HPG) axis

The gonadotropin axis was evaluated by measuring estradiol, FSH, and LH in women and testosterone in men. At follow-up after 6 months, 14/52 (27%, 12 men and 2 women) patients with TBI and 14/34 (41%, 3 men and 11 women) with aSAH had low gonadotropin levels indicating secondary hypogonadism, and at follow-up after 12 months this was seen in 11/52 (21%, 9 men and 2 women) patients with TBI and 8/35 (23%, 3 men and 5 women) with aSAH (Figure 7). Replacement therapy with testosterone was clinically indicated in 2 patients with TBI and in 2 patients with aSAH after 12 months. All women with secondary hypogonadism were postmenopausal, and none of them were treated with oestrogen.

Figure 7: Pituitary deficiency within the first year after TBI and aSAH

![Pituitary deficiency graph]

Prolactin

Hyperprolactinemia was seen in 3 (6%) patients with TBI and none (0%) with aSAH at follow-up after 6 months and in 4 (8%) patients with TBI and 4 (11%) with aSAH at 12 months.

Low PRL levels were seen in 1 (2%) patient with TBI and 1 (3%) with aSAH at follow-up after 6 months and in 2 (4%) patients with TBI and 0 (0%) with aSAH at 12 months.

Antidiuretic hormone

In the acute stage, 43 (80%) patients with TBI and 31 (89%) with aSAH had P–Na>146 and S-osmolality>300 mOsm/kg. Of these, 7 TBI and 15 aSAH patients had been treated with fludrocortisone, and 4 patients with TBI and 8 with aSAH had been treated with desmopressin.

In the acute stage, 5 (9%) patients with TBI and 1 (3%) with aSAH had low P-Na ≤136 in combination with S-osmolality ≤279 mOsm/kg. Three patients with TBI lost weight (−7.3 to
–2.4 kg) and 2 increased in weight (+1.5 to +5.8 kg), while one patient with aSAH lost weight (–1.4 kg).

During follow-up, transient perturbations in P-Na, S-osmolality and BMI were seen in a few patients, but the number of patients was too few to draw any statistical conclusions.

**Pituitary deficiency of any axis over time**

Deficiencies in one or more axes were diagnosed in 15 (27%) patients with TBI in the acute stage, in 6 (11%) after 3 months, in 17 (33%) after 6 months, and in 17 (32%) after 12 months. During the first year after the event, both the disappearance and new onset of PD was observed. Between the acute stage and 3 months follow-up after TBI there were 3 cases of persistent PD, 12 cases of disappearance and 3 cases of new onset of PD; between 3 and 6 months follow-up there were 2 cases of persistent PD, 4 cases of disappearance, and 15 cases of new onset of PD; and between 6 and 12 months follow-up there were 12 cases of persistent PD, 4 cases of disappearance, and 5 cases of new onset of PD. Changes in the individual axes for patients with TBI are presented in Table 14. In patients with aSAH deficiencies in one or more axes were diagnosed in 10 (29%) patients in the acute stage, in 1 (3%) after 3 months, in 17 (50%) after 6 months, and in 11 (31%) after 12 months. Between the acute stage and 3 months follow-up after aSAH there were no cases of persistent PD, 10 cases of disappearance, and 1 case of new onset of PD; between 3 and 6 months follow-up there were 1 case of persistent PD, 0 cases of disappearance, and 16 cases of new onset of PD; and between 6 and 12 months follow-up there were 9 cases of persistent PD, 8 cases of disappearance, and 2 cases of new onset of PD. Changes in the individual axes for patients with aSAH are presented in Table 14.

**Multiple pituitary deficiencies**

Multiple PDs were observed in 4 (7%) patients with TBI in the acute stage, 1 (2%) after 3 months follow-up, 1 (2%) after 6 months follow-up and 2 (4%) after 12 months follow-up. In patients with aSAH, multiple PDs were observed in 3 (9%) patients in the acute stage, none after 3 months follow-up, 2 (6%) after 6 months follow-up, and 1 (3%) after 12 months follow-up.
Table 14: Deficiencies in the different endocrine axes over time in patients with TBI and aSAH

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Axis</th>
<th>Baseline 10 days n (%)</th>
<th>3 months follow-up n (%)</th>
<th>6 months follow-up n (%)</th>
<th>12 months follow-up n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline 10 days n (%)</td>
<td>3 months follow-up n (%)</td>
<td>6 months follow-up n (%)</td>
<td>12 months follow-up n (%)</td>
</tr>
<tr>
<td>TBI</td>
<td>Thyroid</td>
<td>13 (24%)</td>
<td>4 (7%)</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Adrenal</td>
<td>6 (11%)</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td></td>
<td>Somatotropic</td>
<td>Not tested</td>
<td>Not tested</td>
<td>2 (4%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td></td>
<td>Gonadal</td>
<td>Not tested</td>
<td>Not tested</td>
<td>14 (27%)</td>
<td>11 (21%)</td>
</tr>
<tr>
<td></td>
<td>Multiple</td>
<td>4 (7%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>aSAH</td>
<td>Thyroid</td>
<td>8 (23%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td></td>
<td>Adrenal</td>
<td>5 (15%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Somatotropic</td>
<td>Not tested</td>
<td>Not tested</td>
<td>3 (9%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td></td>
<td>Gonadal</td>
<td>Not tested</td>
<td>Not tested</td>
<td>14 (41%)</td>
<td>8 (23%)</td>
</tr>
<tr>
<td></td>
<td>Multiple</td>
<td>3 (9%)</td>
<td>0 (0%)</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Pituitary deficiency during the first year after TBI or aSAH in relation to acute injury variables

In patients with TBI and somatotropic deficiency, we observed higher serum levels of S100B (p = 0.003), and in patients with TBI and thyroidal deficiency, we observed longer hospitalisation in the NICU (p = 0.004). In patients with aSAH and gonadal deficiency, we observed higher median GCS (p = 0.022). No other relations between hormonal deficiencies and acute injury variables were observed in either group.

4.3 PAPER III

4.3.1 Study population

The study population was the same as for Paper II.

4.3.2 Cognitive and affective outcome

The Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS)
Equally large proportions of patients with TBI and aSAH were unable to perform the BNIS at 3 months (27% and 29%, respectively, p = 0.852), 6 months (20% and 18%, respectively, p = 0.753), and 12 months (18% and 14%, respectively, p = 0.655) post-event because some failed the pre-screen test (at 3 months 7 patients with TBI and 8 with aSAH, at 6 months 9 patients with TBI and 5 with aSAH, and at 12 months 8 patients with TBI and 4 with aSAH) and some were not even able to be pre-screened due to ongoing DOC (at 3 months 8 patients with TBI and 2 with aSAH, at 6 months 2 patients with TBI and 1 with aSAH, and at 12 months 2 patients with TBI and 1 with aSAH) (Figure 8).

The BNIS was performed in 73% patients with TBI and 71% with aSAH at 3 months, 80% and 82%, respectively, at 6 months, and 82% and 86%, respectively, at 12 months. The proportions of patients with TBI and aSAH who could perform the BNIS were equal at 3 months (p = 0.853), 6 months (p = 0.753) and 12 months (p = 0.655) post-event.

Among those who performed the BNIS, cognitive dysfunction (cut-off: T-points <40 (<−1 SD)) was seen in 63% of patients with TBI and 76% with aSAH at 3 months, in 54% and 70%, respectively, at 6 months, and 36% and 59%, respectively, at 12 months (Figure 8). Differences in proportions of patients with TBI and aSAH below the cut-off were not significant at 3 months (p = 0.287), 6 months (p = 0.160), or 12 months (p = 0.057) post-event. Median BNIS T-scores were lower after aSAH than after TBI, but the difference was not significant between the groups at 3 months (p = 0.064), 6 months (p = 0.069) or 12 months (p = 0.148) post-event.

Figure 8: Numbers and proportions of patients with TBI and aSAH who failed the pre-screen and result of BNIS T-points who performed BNIS and change of results over time. The cut-off for cognitive dysfunction was T-points <40.
Only 37 patients with TBI and 22 with aSAH had performed BNIS at three time points, and these data were used for the analyses of change over time.

For the TBI group, the BNIS T-scores improved significantly from 3 to 12 months ($p = 0.001$), and this was also significant when analysing the moderate injury ($p = 0.017$) and severe injury ($p = 0.008$) groups separately. Improvement from 3 to 6 months was significant for the whole group ($p = 0.003$) and the severe injury group ($p = 0.019$), but improvements from 6 to 12 months were not significant in any group. For the aSAH group, the BNIS T-scores improved significantly from 3 to 12 months ($p = 0.004$), and this was also significant when analysing the moderate injury ($p = 0.028$) and severe injury ($p = 0.037$) groups separately. Improvement from 3 to 6 months was significant for the whole group ($p = 0.017$) and the moderate injury group ($p = 0.046$), and improvement from 6 to 12 months was significant for the whole group ($p = 0.010$).

According to the GEE, the change of BNIS T-scores over time from 3 to 12 months did not differ significantly between the TBI and aSAH groups ($p = 0.591$). However, there was a trend towards delayed recovery in the aSAH group, which is in accordance with the finding of significant, continued improvement from 6 to 12 months after aSAH but not after TBI.

BNIS T-scores were significantly correlated with GCS for TBI ($r = 0.453$, $p < 0.001$), but not for aSAH ($r = 0.045$, $p = 0.720$). For aSAH, BNIS T-score was neither correlated to Hunt–Hess scores ($r = –0.117$, $p = 0.35$) nor to Fischer scores ($r = –0.149$, $p = 0.233$).

BNIS T-scores were correlated to age in the TBI group ($r = –0.450$, $p < 0.001$), but not in the aSAH group ($r = 0.029$, $p = 0.817$). There was no correlation between BNIS T-scores and gender for the TBI group ($p = 0.400$) or the aSAH group ($p = 0.169$).

In the analyses of the BNIS subscales, the age groups 60–69 and 70–87 years were merged due to the low number of BNIS results in the oldest age group ($n = 1–2$).

For the TBI group, some subscales (Table 15) improved significantly from 3 to 12 months and from 3 to 6 months only in the younger group. For the aSAH group, some subscales (Table 15) improved significantly from 3 to 12 months and from 6 to 12 months in the younger group, but in the older group only orientation improved significantly from 3 to 6 months.
Table 15: Change of BNIS subscales over time for patients with TBI and aSAH.

<table>
<thead>
<tr>
<th>TBI</th>
<th>aSAH</th>
</tr>
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<tbody>
<tr>
<td>age group</td>
<td>age group</td>
</tr>
<tr>
<td>18–59 years</td>
<td>60–87 years</td>
</tr>
<tr>
<td>3 to 6 months</td>
<td>orientation p = 0.034*</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>6 to 12 months</td>
<td>memory p = 0.028*</td>
</tr>
<tr>
<td></td>
<td>awareness p = 0.034*</td>
</tr>
<tr>
<td>3 to 12 months</td>
<td>language p = 0.031*</td>
</tr>
<tr>
<td></td>
<td>awareness p = 0.011*</td>
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***p < 0.001, ** p < 0.01, *p < 0.05

Rancho Los Amigos Cognitive Scale–Revised (RLAS–R)

The RLAS-R scores improved significantly after TBI and aSAH from 3 to 6 months, from 6 to 12 months, and from 3 to 12 months (p < 0.001). After 12 months, patients with TBI had a lower proportion (45%) of patients with “inferior cognitive functioning” compared to patients with aSAH (60%) (Figure 9), but the difference was not significant. We found strong correlations between BNIS T-scores and RLAS-R at 12 months for both TBI (r = 0.750, p < 0.001) and aSAH (r = 0.716, p < 0.001).

Figure 9: Proportion of patients with superior and inferior cognitive functioning outcome after TBI and aSAH

Hospital Anxiety and Depression Scale (HADS)

We found similar proportions of patients with TBI and aSAH above the cut-off for mild or moderate depression at 12 months (9 (22%) patients with TBI and 7 (23%) with aSAH)
(Figure 10), and similar proportions of patients with TBI and aSAH above the cut-off for mild-severe anxiety at 12 months (12 (29%) patients with TBI and 6 (20%) with aSAH) (Figure 11). HADS-D and HADS-A scores did not differ significantly between any of the time points after TBI or aSAH.

Figure 10: Proportions of patients with mild, moderate, and severe depression after TBI and aSAH

![HADS depression](image)

Figure 11: Proportions of patients with mild, moderate, and severe anxiety after TBI and aSAH

![HADS anxiety](image)

We found negative weak correlations between BNIS T-scores and HADS-D scores at 3 (r = −0.506, p = 0.002) and 12 months (r = −0.396, p = 0.018) and between BNIS T-scores and HADS-A at 3 (r = −0.446, p = 0.006) and 12 months (r = −0.412, p = 0.014), but not at 6
months after TBI. We found no correlations between BNIS T-scores and HADS-D or HADS-A at 3, 6, or 12 months after aSAH.

### 4.3.3 Activities of daily living

**Barthel Index (BI)**

BI improved significantly over time except for patients with aSAH from 6 to 12 months. At 12 months, we found equal proportions of those considered totally independent after TBI (59%) and after aSAH (60%) (p = 0.919). We found moderate correlations between BNIS T-scores and BI at 12 months for both TBI (r = 0.565, p < 0.001) and aSAH (r = 0.678, p = 0.001).

### 4.3.4 Global outcome

**Glasgow Outcome Scale Extended (GOSE)**

The GOSE score improved significantly after both TBI and aSAH. At 12 months, we found equal proportions of “favourable” (GOSE 5–8) and “unfavourable” (GOSE 1–4) outcomes after TBI (62% and 38%, respectively) and aSAH (63% and 37%, respectively) (p = 0.919) (Figure 12).

**Figure 12**: Proportion of patients with favourable and unfavourable outcomes after TBI and aSAH

![Graph showing GOSE outcomes](image)

We found a moderate correlation between BNIS T-scores and GOSE scores at 12 months after TBI (r = 0.694, p < 0.001) and a strong correlation at 12 months after aSAH (r = 0.751, p < 0.001).

**EQ-5D**

The EQ-5D index improved significantly after TBI from 3 months to 12 months (p = 0.034), but not between the other time points after TBI or aSAH.
The EQ-5D VAS improved significantly after aSAH from 3 months to 12 months (p = 0.007), but not between the other time points after TBI or aSAH.

4.3.5 Quality of life

LiSat-11

No significant differences in satisfaction with life were seen at 3, 6, or 12 months post TBI (p = 0.730) or aSAH (p = 0.185)

After 3 months, similar proportions of patients with TBI (37%) and aSAH (54%) were satisfied or very satisfied with life “as a whole” (p = 0.180), and similar proportions of patients with TBI (63%) and with aSAH (46%) reported different degrees of dissatisfaction (p = 0.180). At 6 months we found similar proportions of patients with TBI and aSAH (43% and 40%, respectively) who were satisfied or very satisfied with life (p = 0.862), while 60% of patients with TBI and 57% with aSAH reported different degrees of dissatisfaction (p=0.862). At 12 months, similar proportions of patients with TBI (39%) and with aSAH (43%) were satisfied or very satisfied with life (p = 0.287), and similar proportions of patients with TBI (61%) and with aSAH (57%) reported different degrees of dissatisfaction (p = 0.287) (Figure 13).

Changes in satisfaction with life were not significant between 3, 6, or 12 months after TBI (p = 0.730) or aSAH (p = 0.185), nor were changes in satisfaction in the 10 specific domains. There was no correlation between BNIS T-scores and LiSat 1 for TBI or aSAH at 3, 6, or 12 months post-event.

Figure 13: Proportions of patients who were satisfied and unsatisfied with life after TBI and aSAH
4.4 PAPER IV

4.4.1 Study population
We included 127 patients (82 with TBI and 45 with aSAH), but 36 (26 with TBI and 10 with aSAH) dropped out (reason presented earlier in the description of Paper II). Of the 91 patients (56 with TBI and 35 with aSAH), 49 were men and 42 women, with a mean age of 51.0 ±15.2 years, and 66 patients had severe brain injury and 25 patients had moderate brain injury according to the admission GCS score (median 6, Q1–Q3 (4–9)).

There was no significant difference between patients with TBI or with aSAH regarding GCS scores (p = 0.144) and BMI (p = 0.893), while there was significant difference in age (p = 0.001) and gender (p < 0.001).

4.4.2 Impact of hormone disturbance on cognitive and global outcome 12 months post-event and in relation to baseline characteristics
We created subgroups of patients who showed any hormonal disturbance at any of the tests at 10 days or at follow-up after 3, 6, and 12 months post-event (low or high hormone level) and those who did not (normal hormone level).

BNIS and pituitary disturbance

*Thyroid axis*

Patients with high thyroid hormone levels had significantly lower BNIS T-scores (p = 0.018) compared to those with normal thyroid levels and these patients were significantly older (p = 0.016), but other baseline variables did not differ between the subgroups. Multiple linear regression analysis demonstrated a significant negative association between BNIS T-score and age (b = −0.44, p = 0.027, CI: −0.83−−0.05), and a significant positive association with GCS (b = 1.48, p = 0.036, CI: 0.10−2.7), but not with gender or high and low thyroid hormone. Thyroid hormone level, age, GCS and gender explained 20.4% of the variance of the BNIS T-scores (adjusted R² = 0.204).

*Somatotropic axis*

Patients with high IGF-I levels had significantly lower BNIS T-scores (p = 0.012) compared to those with normal IGF-I levels and these patients were significantly older (p = 0.021), but other baseline variables did not differ between the subgroups. Multiple linear regression analysis demonstrated a significant negative relationship between BNIS T-score and age (b = −0.49, p = 0.011, CI: −0.87−−0.12), and a significant positive association with GCS (b = 1.42, p = 0.042, CI: 0.05−2.79), but not with gender or high or low IGF-I. IGF-I level, age, GCS, and gender explained 17.1% of the variance of the BNIS T-scores (adjusted R² = 0.171).

*Prolactin*

Patients with low PRL levels had significantly lower BNIS T-scores (p = 0.027) compared to those with normal PRL levels. There were no differences between baseline variables in any
subgroups. Multiple linear regression analysis demonstrated significant negative relationships between BNIS T-score and age (b = −0.51, p = 0.005, CI: −0.87−−0.16) and low PRL (b=−31.02, p = 0.016, CI: −56.15−−5.89), and a significant positive association with GCS (b = 1.35, p = 0.043, CI: 0.04−2.65), but not with gender or with high PRL. PRL level, age, GCS and gender explained 23.6% of the variance of the BNIS T-scores (adjusted R² = 0.236).

Adrenal axis and gonadal axis

BNIS T-scores did not differ between subgroups with different cortisol or gonadotropin levels.

Multiple axes

Multiple linear regression analysis demonstrated no relationship between BNIS T-scores and low or high hormone levels.

RLAS-R and pituitary disturbance

Thyroid axis

Patients with high thyroid hormone levels had significantly lower RLAS-R scores (p = 0.026) compare to those with normal thyroid hormone levels, and these patients were significantly older (p = 0.011), but other baseline variables did not differ between the subgroups. Multiple linear regression analysis demonstrated a significant positive relationship between RLAS-R score and GCS (b = 0.14, p = 0.020, CI: 0.02−0.26), but not with age, gender, or low or high thyroid hormone. Thyroid hormone level, age, GCS, and gender explained 16.6% of the variance of the RLAS-R scores (adjusted R² = 0.166).

Somatotropic axis

Patients with high IGF-I levels had significantly lower RLAS-R score (p = 0.006) compared to those with normal IGF-I levels and these patients were significantly older (p = 0.019), but other baseline variables did not differ between the subgroups. Multiple linear regression analysis demonstrated a significant positive relationship between RLAS-R score and GCS (b = 0.13, p = 0.019, CI: 0.02−0.24), and a negative association with high IGF-I (b = −1.78, p = 0.002, CI: −2.87−−0.70), but not with age, gender, or low IGF-I. IGF-I level, age, GCS, and gender explained 24.3% of the variance of the RLAS-R scores (adjusted R² = 0.243).

Prolactin

Patients with high PRL levels had significantly lower RLAS-R scores (p = 0.025) compared to those with normal PRL levels. There were no differences between baseline variables in any subgroups. Multiple linear regression analysis demonstrated significant negative relationships between RLAS-R score and age (b = −0.040, p = 0.013, CI: −0.071−−0.009) and high PRL (b = −1.42, p = 0.034, CI: −2.73−−0.11), and a significant positive relationship with GCS (b = 0.12, p = 0.037, CI: 0.01−0.23), but not with gender or low PRL. PRL level, age, GCS and gender explained 18.2% of the variance of the RLAS-R scores (adjusted R² = 0.182).
Adrenal and gonadal axis

RLAS-R score did not differ between subgroups with different cortisol or gonadal levels.

Multiple axes

Multiple linear regression analysis demonstrated no relationship between RLAS-R scores and low or high hormone levels.

GOSE and pituitary disturbance

Thyroid axis

Patients with high thyroid hormone levels had significantly lower GOSE scores (p = 0.011) compared to those with normal thyroid hormone levels, these patients were significantly older (p = 0.011), but other baseline variables did not differ between the subgroups. Multiple linear regression analysis demonstrated a significant negative relationship between GOSE score and age (b = –0.04, p = 0.004, CI: –0.07—–0.01), but not with gender, GCS, peak S100B, acute pupil light reaction, or low or high thyroid hormone. Thyroid hormone level, age, GCS and gender explained 21.2% of the variance of the GOSE scores (adjusted R² = 0.212).

Gonadal axis

Patients with low gonadotropin level had significantly lower GOSE scores (p = 0.011) compared to those with normal gonadotropin levels, and these patients were significantly older (p = 0.013), but other baseline variables did not differ between the subgroups. Multiple linear regression analysis demonstrated significant negative relationships between GOSE score and age (b = –0.05, p = 0.001, CI: –0.03—–0.02), and low gonadotropins levels (b = –0.80, p = 0.033, CI: –1.54—–0.07), and a significant positive relationship with GCS (b = 0.11, p = 0.025, CI: 0.01–0.21), but not with gender. Gonadotropin level, age, GCS and gender explained 24.5% of the variance of the GOSE scores (adjusted R² = 0.245).

Prolactin

Patients with high PRL levels had significantly lower GOSE score (p = 0.022) compared to those with normal prolactin levels. There were no differences between baseline variables in any subgroups. Multiple linear regression analysis demonstrated significant negative relationships between GOSE score with age (b = –0.05, p < 0.001, CI: –0.08—–0.03), and high PRL (b = –1.49, p = 0.006, CI: –2.55—–0.43), but not with gender, GCS or low PRL. PRL level, age, GCS and gender explained 25.5% of the variance of the GOSE scores (adjusted R² = 0.255).

Adrenal and somatotropic axis

GOSE scores did not differ significantly between subgroups of patients with different cortisol or IGF-I levels.
Multiple axes

Multiple linear regression analysis showed no relationship between GOSE scores and low or high hormone levels.
5 DISCUSSION

Although the number of participants in the studies included in this thesis was modest, the data set based on repeated, systematic evaluations during the first year after the event is comprehensive and allows some conclusions to be drawn. Thus, we believe that the overall aim of this thesis – to increase our knowledge about pituitary insufficiencies and their potential impact on clinical outcome after TBI or aSAH – has been fulfilled. Some of the results lend support to corresponding results of other studies, that have been published in recent years, and some add new information and raise other questions for further research as will be discussed.

5.1 PITUITARY DYSFUNCTION AFTER TRAUMATIC BRAIN INJURY OR ANEURYSMAL SUBARACHNOID HAEMORRHAGE

In the studied population of 84 patients with TBI and 46 with aSAH, endocrine assessment was done in all patients in the acute phase. Follow up assessments at 3, 6, and 12 months were performed in 56 TBI and 35 aSAH patients. Endocrine abnormalities occurred at all four assessment times. In our study, we assessed two hormonal axes in the acute stage and after 3 months, but after 6 and 12 months we assessed four hormonal axes. The somatotropic axis was evaluated based on IGF–I. In summary, PD was seen in 27% patients with TBI in the acute stage, in 11% after 3 months, in 33% after 6 months, and in 32% after 12 months. In patients with aSAH pituitary disturbances were seen in 29% in the acute stage, in 3% after 3 months, in 50% after 6 months, and in 31% after 12 months. Overall, these figures are in agreement with the findings in other, recent reviews in this area.

5.1.1 Pituitary dysfunction in acute phase after traumatic brain injury or aneurysmal subarachnoid haemorrhage

Anterior pituitary function

In the acute stage we investigated only the adrenal and thyroid axis between day 1 and day 15 post-event. Our study of 130 patients showed that 12% of patients with TBI and 14% with aSAH had hypoadrenalism with a cortisol cut-off value of <550 nmol/L at 30 minutes after the SST. Thyroid hormone dysfunction was interpreted as low fT4 in combination with normal or low TSH and we observed this in 17% of patients with TBI and 20% with aSAH. Other TBI studies conducted by Agha et al [114] on moderate and severe injury found insufficient cortisol and thyroid hormone levels in 16% and 2% of patients, respectively, while Klose et al [106] observed insufficient cortisol and thyroid hormone levels in 33% and 4% of patients with mild and severe injury, respectively. aSAH studies by Tanriverdi et al [123] showed insufficient cortisol and thyroid hormone levels in 23% and 0% of patients, respectively, but Kronvall et al [157] found insufficient levels in 8% and 6% of patients, respectively. Differences in prevalence of PD might depend on different criteria for diagnosis of hormone insufficiencies and different dynamic tests. Klose et al [106] used the ITT and the SST and defined adrenal insufficiency as cortisol < 550nmol/L at 30 minutes in both tests, but Tanriverdi et al [123] defined hypoadrenalism when basal cortisol was <193 nmol/L.
Agha et al [114] defined thyroid dysfunction when fT4 and TSH was below the normal reference range. Our study also showed high fT4 in 10% of patients with TBI and 16% with aSAH and that 35% of patients with TBI and 53% with aSAH had an exaggerated cortisol response in the SST of >1,000 nmol/L (max 3,300 nmol/L). Low fT3 was seen in 32% of patients with TBI and 42% with aSAH. Factors that potentially can influence hormone levels are the use of glucocorticoids, the physiological reaction to the stress caused by the trauma, and severe medical illness. During acute critical illness, increased plasma concentrations of ACTH, cortisol, TSH, T4, GH and PRL, which together with low gonadotropin hormones and low T3 syndrome have been described as part of important adaptive stress responses in the early phases following severe medical illness [102], but during the prolonged phase, adrenal cortisol synthesis and secretion can be affected by cytokines, causing functional adrenal insufficiency. It is not clear to what extent the hormone deficiencies that we and others have reported are secondary to structural hypothalamic–pituitary injury or reflect adaptive mechanisms to acute illness. It is possible that it is a multitude of combinations of all these factors that explain the different frequencies of PiD described in the literature.

**Posterior pituitary function**

During the time in the NICU, many patients with TBI and aSAH had high P-Na in combination with high S-osmolality, but only 8% of patients with TBI and 22% with aSAH were treated with desmopressin. Other researchers have reported frequencies of ADH deficiency between 0% [106] and 26% [122] in the acute stage after TBI, while no such deficiency was observed after aSAH [157]. Low P-Na in combination with low S-osmolality was observed in 12% patients with TBI and 4% with aSAH. No clear distinction between CSW and SIADH could be made. Again, the differences between our findings and the previously reported findings probably relate to differences in study populations and their treatments.

### 5.1.2 Pituitary dysfunction during the first year after traumatic brain injury or aneurysmal subarachnoid haemorrhage

#### Adrenal dysfunction

In the patients with TBI who completed the study, 11% had adrenal insufficiency in the acute stage, 6% after 3 months, 2% after 6 months, and 4% after 12 months post-event. In patients with aSAH, 15% had adrenal insufficiency in the acute stage, 0% after 3 months, 3% after 6 months, and 0% after 12 months post-event. In summary, our results show a decrease in adrenal insufficiency over time in accordance with the findings in some studies of TBI and aSAH. Other researchers have reported frequencies of adrenal insufficiency after TBI between 4% [125] and 19% [107] after 3 months, between 0% [125] and 23% [109] after 6 months, and between 7% [106, 110] and 19% [109, 120] after 12 months post-event. With regards to frequencies of adrenal insufficiency after aSAH other researchers have reported between 3% [110] and 21% [140] after 3 months, 20% [157] after 6 months, and between 0% [137] and 11% [135] after 12 months post-event. Differences in prevalence of adrenal
deficiency might depend on different criteria for diagnosing hormone dysfunction and different dynamic tests. Kronvall et al [135] and Klose et al [106] used the ITT. Another confounder might be that 7 patients with TBI and 3 with aSAH, 3 with TBI and 4 with aSAH, and 7 with TBI and 4 with aSAH refused to undergo the dynamic tests or did not come to the appointment at 3, 6, and 12 months, respectively.

We observed hypercortisolism only in the acute stage in 53% of patients with TBI and 56% with aSAH. In the study by Marina et al [126], hypercortisolism was seen in 34% of patients with TBI, but the difference is that in their study the endocrine assessment was done between 2 and 5 months post injury. We interpret the high levels of cortisol as a result of the acute stressful situation, especially because such levels were only seen in the acute stage measurements.

**Thyroid hormone dysfunction**

In the patients with TBI who completed the study, thyroid hormone deficiency was seen in 24% in the acute stage, in 7% after 3 months, in 4% after 6 months, and in 0% after 12 months post injury. Other researchers have reported frequencies of adrenal insufficiency after TBI between 0% [125] and 8% [107] after 3 months, between 0% [125] and 4% [106] after 6 months, and between 2% [106] and 6% [120] after 12 months post injury. In the patients with aSAH who participated in the entire study, thyroid hormone deficiency was seen in 23% in the acute stage, in 3% after 3 months, in 3% after 6 months, and in 6% after 12 months post-event. Other researchers have reported frequencies of thyroid hormone deficiency after aSAH between 0% [140] and 9% [110] after 3 months, 0% [157] after 6 months, and between 0% [137, 196] and 9% [110] after 12 months post-event. Thus, similar to previous results we found a decrease in the number of patients with HP.

We observed hyperthyroidism in 4–8% of patients with TBI and 3–17% of patients with aSAH during the first year post-event. Olivecrona et al [160] observed elevated fT4 in 9% of patients at day 1 after severe TBI. The hyperthyroidism did not elicit any obvious clinical symptoms and was probably a physiological adaptation to the overall clinical situation and the treatment given.

**Growth hormone dysfunction**

In the patients with TBI who completed the study, low IGF-I levels were seen in 4% after 6 months and in 12% after 12 months post injury, but with aSAH low IGF-I levels were seen in 9% after 6 months and in 6% after 12 months post-event. Other researchers have reported frequencies of somatotroph insufficiency after TBI between 13% [106, 109] and 18% [197] after 6 months and between 10% [107, 109] and 38% [120] after 12 months post injury. Other researchers have reported frequencies of somatotroph insufficiency after aSAH of 20% [157] after 6 months, and between 0% [137] and 29% [135] after 12 months post-event. Differences in prevalence of somatotroph deficiency might depend on different criteria for the diagnosis of hormone dysfunction. Kelly et al [197], Klose et al [106, 137], and Kronvall et al [135] all
used the GHRH-ARG stimulation test. In our study, the GHRH-ARG stimulation test was performed at 12 months follow-up if IGF-I < −2SD, but a normal reference range of IGF-I level does not exclude GH deficiency because about 30% of patients with GH deficiency have IGF-I levels within the normal reference range [155], and as previously mentioned the results might be confounded by drop-outs (2/6 patients with TBI and 2/2 with aSAH refused to undergo the dynamic test or did not come to the appointment at 12 months follow-up).

In the patients with TBI, high IGF-I levels were seen in 17% after 6 months and in 14% after 12 months post injury and in the patients with aSAH high IGF-I levels were seen in 12% after 6 months and 3% after 12 months post-event. In the study by Marina et al [126], elevated IGF-I was seen in 26% of patients with TBI after 2–5 months post injury. IGF-I is a non-specific marker of GH deficiency, and the levels of IGF-I are dependent on nutritional status, binding proteins, liver function, and several pharmacological agents. The influence of these was not studied in detail but all might have played a role in the observed levels of IGF-I.

**Gonadotropin insufficiency**

Gonadal insufficiency was observed in 27% of patients with TBI after 6 months and in 21% after 12 months post injury. In the patients with aSAH gonadal insufficiency was observed in 41% after 6 months and in 23% after 12 months post-event. Our results are in accordance with the findings in other studies of TBI and aSAH in which frequencies of gonadal insufficiency after TBI varied between 11% [125] and 23% [109] after 6 months and between 8% [123] and 21% [107] after 12 months post injury. Other researchers have reported gonadal insufficiency after aSAH in 2% [157] after 6 months, and between 0% [137] and 11% [135] after 12 months post-event.

**Prolactin**

We found hyperprolactinemia in 6% of patients with TBI after 6 months and in 8% after 12 months post injury. In the patients with aSAH hyperprolactinemia was seen in 0% after 6 months and in 11% after 12 months post-event. Our results are in accordance with the findings in previous studies of TBI and aSAH where frequencies of hyperprolactinemia after TBI were reported to be between 2% [106] and 15% [109] after 6 months, and between 2% [106] and 13% [109] after 12 months post injury, but frequencies after SAH were 2% [157] after 6 months and between 0% [140] and 5% [135] after 12 months post-event.

**Antidiuretic hormone**

During follow-up, no single case of DI or SIADH was observed. Other researchers have reported frequencies of DI after TBI between 2% [110] and 4% [125] after 3 months, between 2% [125] and 8% [122] after 6 months, and between 3% [110] and 6% [122] after 12 months after injury, but after aSAH the frequencies of DI were between 0% [157] and 6% [110] after 3 months, 0% [157] after 6 months, and between 0% [135] and 3% [110] after 12 months post-event. Thus, the posterior pituitary lobe seems more robust to trauma.
5.1.3 Development over time

Our study showed that PiD was more common early after the injury but might occur in a substantial proportion of patients at later phases. Our data also show that in most cases anterior pituitary hormone abnormalities were new, some had resolved at follow-up compared to the acute stage, and some occurred later during follow-up. Similar results have also been observed in other longitudinal studies [108-110, 120, 123, 125, 141]. Acute phase hormone dysfunction that later resolves might represent adaptations to acute critical illness [102]. ICP or hypothalamopituitary oedema might cause transitory pituitary dysfunction, which resolves as the patient’s condition improves. Another suggested mechanism might be the regeneration of damaged pituitary portal vessels that grow into the surviving parts of the pituitary gland, thus supporting tissue regeneration and the return of function [150]. Mechanisms behind the development of PiD in later phases might be that initial hormone dysfunctions have been masked by an acute neuroendocrine response to severe disease or might reflect delayed secondary injury.

5.1.4 Relation to traumatic brain injury or aneurysmal subarachnoid haemorrhage characteristics

The relationship between endocrine dysfunction and clinical TBI or aSAH characteristics was investigated in the acute stage and during the first year post-event.

In the acute stage, patients with TBI and adrenal insufficiency more often had brain oedema on CT-scan compared with those who had normal cortisol function. This finding agrees with findings by Bavisetty et al [125], who observed a greater occurrence of diffuse brain swelling on CT-scan at 6–9 months after TBI in patients with major hormonal deficiencies, and by Krahulik et al [108], who found that brain oedema and cranial base fracture were risk factors for pituitary insufficiency in TBI patients. We observed that in the acute stage, patients with TBI and thyroid insufficiency more often had traumatic SAH on CT-scan compared with patients with normal thyroid function, which is in contrast to the TBI study by Bavisetty et al [125].

During the first year post-event, we observed that patients with aSAH and gonadotropin insufficiency had significantly higher GCS scores, while Klose et al [137] found that in patients with aSAH the presence of early hormonal insufficiency was associated with a lower GCS score, but not with Fisher grade or Hunt & Hess grade. Agha et al [109] in a study of TBI patients found no significant relation between adrenal and somatotroph insufficiency and GCS score. Thus, injury severity according to these conventional, clinical severity markers do not seem to be consistently associated with pituitary dysfunction. We also found that patients with TBI and thyroid insufficiency had significantly longer length of stay in the NICU, and patients with TBI and somatotroph insufficiency had a significantly higher peak serum level of S100B.
5.2 OUTCOME AFTER TRAUMATIC BRAIN INJURY OR ANEURYSMAL SUBARACHNOID HAEMORRHAGE

We compared the course and outcome of cognitive impairments during the first year after TBI or aSAH and explored the association with global outcome. Outcomes at 12 months were not significantly different between TBI and aSAH. Cognitive outcome was graded according to the BNIS. This instrument is commonly used to screen cognitive disturbances after ABI, both TBI and stroke. This instrument was validated in a Swedish population and has good sensitivity and specificity [178].

5.2.1 Change in BNIS T-scores over time

BNIS T-scores did not differ significantly between diagnostic groups, and the proportion of patients with cognitive impairments was not significantly different at any time point. We found that median BNIS T-scores improved significantly both early (3–6 months) and late (6–12 months) after aSAH while improvements after TBI were significant only during the early phase post-event. Our results in patients with TBI are in agreement with the findings in a study by Stenberg et al [198] of patients with severe TBI where BNIS T-scores improved the most within 3 months after the injury. Millis et al [199] showed that cognitive function improved even years after TBI, but these improvements might require longer study periods and/or more extensive neuropsychological assessments to detect. The majority of patients with TBI and aSAH had a severe injury, and recovery after severe aSAH was delayed compared with severe TBI. Several factors might explain such a differential time course of recovery, including different character of the primary brain lesion such a diffuse axonal injury in TBI [200] and cerebral infarction after aSAH [91]. There might also be differences with regard to secondary insults as well as neuroplasticity responses.

5.2.2 Change in BNIS subscales over time

Improvement on the separate BNIS subscales varied over time in different age groups and in different diagnostic groups, which hindered conclusions on the relative impact of time on different cognitive domains.

5.2.3 Relations between baseline characteristics and outcome variables.

Age was negatively correlated with BNIS T-scores after TBI, but not after aSAH. Gender had no relation to BNIS T-scores in any diagnostic group.

The acute-phase GCS score was correlated with BNIS T-scores after TBI, but not after aSAH. The GCS was developed for assessment of patients with coma and impaired consciousness after head injury [6] and is mainly used to classify and assess patients with TBI [201] and has predictive value versus global outcome after TBI [202]. However, the GCS has also been recommended for assessment of patients with SAH [203]. In patients with aSAH, we found no correlation between BNIS T-scores and Hunt–Hess scale scores, which was developed to predict the prognosis and outcome of aSAH [35]. Nor were BNIS T-scores
correlated to Fisher scale scores in aSAH, which is in accordance with findings in a previous study by Wong et al [204].

In our study, we found no correlation between BNIS T-scores and HADS in any of the diagnostic groups. Neither anxiety nor depression scores changed from 3 to 12 months after TBI or aSAH, and about 20% of patients in both groups met the criteria for depression or anxiety, which is in agreement with earlier studies [205, 206]. Both depression and anxiety are possible confounders of cognitive function.

We found strong or moderate correlations between BNIS T-scores and outcomes measured with the GOSE or RLAS-R after both TBI and aSAH. This result corresponds with a study of patients with aSAH by Wong et al [207], using the Montreal Cognitive Assessment to assess cognitive function.

We observed no correlation between BNIS T-scores and life satisfaction according to the LiSat 11. LiSat 11 scores did not change over the course of the year post-event in either diagnostic groups, which in line with a previous study of patients with severe TBI [198]. One reason might be that results on the LiSat reflect both emotional, cognitive, and achievement parameters [194] and are related to education, employment, health, and physical activity factors [195].

5.3 IMPACT OF PITUITARY DYSFUNCTION ON OUTCOME AFTER TRAUMATIC BRAIN INJURY OR ANEURYSMAL SUBARACHNOID HAEMORRHAGE

The associations between pituitary dysfunction after TBI and aSAH during the first year after the event and clinical outcome at 12 months were investigated. The most frequent hormonal dysfunctions during the first year after the event were hypogonadotrope hypogonadism (38%) and hypercortisolism (52%). At 12 months, performance on the BNIS, RLAS-r, and GOSE was impaired in 54 %, 51% and 37%, respectively. We found that low levels of gonadal hormones and high levels of somatotropic hormones (IGF-I) and PRL, occurring at any of the four test points during the first year after the event, were independently associated with poorer clinical outcome at 12 months. Regression coefficients indicated that the occurrence of hypogonadotropic hypogonadism during the first year after the event lowered the GOSE score at 12 months by one point. Pituitary dysfunction, age, gender, and GCS explained 16–25% (R^2) of the variation of outcome variables. This means that other factors explain a large part of the variation of outcome.

5.3.1 Associations between abnormal hormone levels and outcome

Low gonadotropins had a significant negative association with the GOSE but not with the BNIS or RLAS-R. Our finding is in agreement with the results of some previous TBI and SAH studies reporting on the impact of multiple hormone dysfunctions including the gonadotrophic axis [138, 142, 157, 158], studies on outcome according to the GOS as well as with a study by Marina et al [126] who also used the GOSE. Another study by Bondanelli et
al [124] reported a negative impact of gonadotropin disturbances on cognitive/behavioural outcome measured with the RLAS-R in patients with TBI, which is in contrast to our study, that also included data from patients with aSAH.

**High IGF-I** had a significant negative association with the RLAS-R, but no association with the BNIS or GOSE. The cause of increased levels of IGF-I as well as of other hormones, as observed in our cohort but not often reported in previous studies, is unknown. Potential causes include somatic stress reactions and complex interactions between the pituitary hormones as previously suggested [160]. Further, nutritional status, binding proteins, liver function, and several pharmacological agents might impact on IGF-I, as mentioned earlier.

**Low IGF-I** had no association with the BNIS, RLAS-R or GOSE. These findings partly agree with findings by Schneider et al [158], who observed no impact of somatotropic dysfunction on the GOS in their study of TBI and aSAH.

**High PRL** levels had a significant negative association with the RLAS-R and GOSE, but not with the BNIS. This is agreement with a study by Marina et al [126] who reported lower GOSE scores in patients with TBI and elevated stress hormones (PRL, IGF-I, and cortisol).

We found no signs of an impact of either abnormal thyroid or cortisol level. These findings are in line with a study of TBI and aSAH by Schneider et al [158] who found no association between corticotrophic dysfunction and GOS scores, and with Olivecrona et al [160] who found that low s–cortisol in the acute stage after severe TBI was not associated with higher mortality or worse GOS score at 3 months post-event. Our findings are in contrast with other studies that found that hypothyroidism, hyperthyroidism, and hypercortisolism might have a negative impact on cognitive function [208, 209]. The differences observed in these studies might be caused by differences in study cohorts, differences in methods, and different interpretations of hormonal analyses.

We found no signs of an impact of either multiple low or high levels of pituitary hormones on outcome. Factors at play might include low frequency of multiple hormone deviations in individual patients at any of the four test points and because of that our results must be interpreted with caution. Our results are in agreement with a study of patients with TBI by Bavisetty et al [125] who found no association between pituitary dysfunction (somatotrophic, gonadotrophic, thyreotrophic, corticotrophic, posterior pituitary axes) and GOSE score.

Our data suggest that global measures such as the GOSE might be more sensitive to the impact of PiD than specific cognitive measures such as the BNIS. This might reflect that impairments other than cognitive impairments, e.g. emotional, motor, or musculoskeletal impairments, are also affected by pituitary dysfunction and add to worse global outcome according to the GOSE.
6 LIMITATIONS

Factors that potentially can influence hormone levels include the use of glucocorticoids and others drugs, physiological reactions to the stress caused by the trauma, and severe medical illness. In addition, infection, raised ICP, seizures, vasospasm, arterial hypotension, hypoxemia, and pyrexia might also affect the hormone levels.

Although our drop-out rate and missing data were modest, there is still a risk for underestimation of pituitary disturbances.

We used the IGF-I level as a marker for GH secretion, and it should be pointed out that an IGF-I level within the normal reference range does not exclude GH deficiency because 30% of patients with GH deficiency have IGF-I levels within the normal reference range [166]. Thus, there is a risk for underestimation of growth hormone deficiency. The GHRH-ARG stimulation test was only performed in patients with IGF-I < –2SD after 12 months, which might increase the risk of underestimating GH deficiency.

It should also be pointed out that reference values might overestimate the true frequency of pituitary dysfunction in brain-injured populations, as recently discussed by Klose et al [145].

The sample size and the fact that patients were included from only one hospital limit generalisability. However, inclusion from only one hospital and follow up within the same health care system should reduce potential confounding effects of varying acute and rehabilitation interventions.

We did not use a comprehensive neuropsychological assessment due to limited study resources. Further, we wanted to apply less demanding assessments and minimise the risk for fatigue during extended assessment sessions.

All assessments were done by the same person. Thus, the risk for systematic bias of scoring must be considered.
7 CONCLUSIONS

- The studies presented in this thesis show that PiDs occur from the acute phase until 12 months after TBI and aSAH. Most of the pituitary disturbances were transient, and only a few patients needed replacement hormonal therapy (two patients were on replacement with hydrocortisone, four men were on testosterone, and one patient was on replacement with growth hormone), and thus it is important to recognise that persistent PiD requiring hormonal replacement might occur in only a minority of patients after TBI or aSAH. Thus, our data support the need for systematic follow-up of pituitary function after moderate or severe TBI or aSAH. (Paper I & II)

- The studies could not identify a marker of increased risk for pituitary deficiency. (Paper I & II)

- We found significant improvements in cognition in patients with TBI and aSAH from 3 to 12 months post-event. Outcomes according to the BNIS, GOSE, and RLAS-R at 12 months were not significantly different between the diagnostic groups, but relatively greater improvement in cognition occurred during the later phase (6 to 12 months) after aSAH compared to TBI. Cognitive function according to the BNIS correlated with cognitive function according to RLAS-R and with global outcome according to the GOSE. (Paper III)

- Acute GCS scores were associated with cognitive function according to the BNIS T-scores after TBI but not after aSAH. BNIS T-scores after aSAH were not related to Hunt and Hess scores or Fisher scores. (Paper III)

- PiD during the first year after TBI and aSAH might have significant effects on clinical outcome at 12 months after the event. The study supports the need for screening of pituitary dysfunction after TBI and aSAH and might support the design of further studies in this area. (Paper IV)
8 SVENSK SAMMANFATTNING

Traumatisit hjärnskada (THS) och pulsåderbråcksblödning i hjärnan (SAB) är vanliga sjukdomar som kan vara livshotande och kan orsaka permanenta fysiska, kognitiva, beteendemässiga och psykosociala funktionshinder som begränsar dagliga aktiviteter. THS och SAB medför en stor risk för skada i hypotalamus och hypofysen, delar av hjärnan som är av stor betydelse för kroppens hormonbalans. Många av de hormonella rubbningar som uppträder ger symtom, som är svåra att skilja från själva hjärnskadans. Oftast är det därför inte möjligt att kliniskt identifiera vilka patienter som utvecklat en hypofyssvikt. Den rapporterade förekomsten av hormonell svikt (hypofyssdysfunktion) efter THS och SAB varierar mellan publicerade studier.

De vetenskapliga arbetena, som utgör denna doktorsavhandling utformades i syfte dels att studera förekomst av hormonella störningar under första året efter THS eller SAB för att öka kunskapen om hypofyssdysfunktion efter THS och SAB och dels att undersöka samband mellan hormonella rubbningar och kognitivt och globalt utfall efter traumatisk hjärnskada och pulsåderbråcksblödning i hjärnan.

I delarbete I och II presenterades resultaten av hormonella störningar under första året efter THS och SAB. Vi fann att hormonella störningar var frekventa tidigt efter THS och SAB men blev färre under det första året av uppföljningen. Av hormonella rubbningar var könshormonsbrist vanligast. Endast ett fåtal patienter behövde hormonell behandling.

I delarbete III presenteras en jämförelse av förloppet av kognitiva funktionsnedsättningar under första året efter THS och SAB och undersöks samband mellan skadegraden och kognitivt respektive globalt utfall. Kognitionen förbättrades signifikant mellan alla tidpunkter i båda grupperna utom mellan 6 och 12 månader efter THS. Vid 12 månader hade liknande proportioner av patienter med THS och SAB gott utfall. Kognitiv nedsättning befanns ha samband med skadegraden vid THS men inte vid SAB.

I delarbete IV presenteras samband mellan hormonella störningar efter THS och SAB, och kognitivt respektive globalt utfall vid 12 månader efter skada. Könshormonbrist och hög prolaktin hade negativt samband med globalt utfall. Studien visade inget samband mellan kognitivt utfall vid 12 månader och förekomsten av hormonella avvikelser.

Sammanfattningsvis visar studierna att påverkan på hypofyssfunktionen förekommer från den akuta fasen till 12 månader efter THS och SAB och ger stöd för behovet av systematisk uppföljning av hypofyssfunktionen efter THS och SAB. Endast ett fåtal patienter utvecklade hypofyssvikt och behövde hormonbehandling. Kognitiva förbättringar efter THS och SAB visade likheter och skadegraden var associerad med kognitivt resultat efter THS men inte SAB. Hormon rubbningar under det första året efter THS och SAB kan påverka det kliniska utfallet vid 12 månader efter skada. Vår studie stöder behovet av systematisk screening av hypofyssfunktionen efter THS och SAB liksom behovet av fortsatta studier inom området.
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