Pituitary Dysfunction and Quality of Life after Subarachnoid Hemorrhage
Pituitary Dysfunction and Quality of Life after Subarachnoid Hemorrhage

Erik Kronvall

DOCTORAL DISSERTATION
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Abstract
Spontaneous subarachnoid hemorrhage (SAH) is an extremely severe condition. Case fatality rates are high and survivors many times face impairments in functional outcome due to neurological and cognitive defects. Mood disorders, fatigue and sleeping disturbances are common. Such sequelae have all been associated with reduced quality of life (QoL). Given similarities with psychological symptoms seen in patients with pituitary dysfunction (PD), the aim of the studies was to investigate the prevalence of endocrine abnormalities of hypothalamic and pituitary origin following SAH and the relationship between PD and QoL. An additional aim was to investigate QoL and reintegration after SAH in a very long time perspective.

For this purpose, a cohort of 51 patients with aneurysmal SAH was followed with repeated assessments of pituitary function and health-related QoL up to 2 years after ictus. Another cohort of 87 patients with spontaneous SAH (54 of aneurysmal origin and 13 of unknown cause) and good neurological outcome was evaluated with questionnaires pertaining to QoL and reintegration 20-28 years after SAH.

Evidence of PD was found in 37% in the acute phase after SAH, in 27% after 3-6 months, in 34% after 6-12 months and in 43% after 12-24 months. Along with age, sex and clinical admission status, PD independently predicted QoL. Patients with PD reported reduced QoL after 3-6 and 6-12 months. This was on account of central hypoadrenalism. In the long-term follow-up cohort, more than half reported persisting reintegration difficulties, but self-assessed QoL was not impaired.

In conclusion, the studies support earlier findings that endocrine abnormalities are common after SAH and that PD, particularly central hypoadrenalism, significantly contributes to reduced QoL. In the time perspective of over 20 years, SAH patients with early good neurological recovery still suffered from reintegration difficulties. In spite of this, QoL assessments equaled those of healthy populations.

Key words: subarachnoid hemorrhage, outcome, pituitary dysfunction, quality of life
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Erik Kronvall
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Faculty of Medicine | Department of Clinical Sciences Lund, Neurosurgery

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To my father, Per Kronvall (1947-2013), whose passion for science and philosophy has been the greatest inspiration.
Content

Original papers ................................................. 11
Abbreviations ............................................... 13

Background .................................................................................................................. 15
Subarachnoid hemorrhage ......................................................................................... 15
  Historical perspective and epidemiology ......................................................... 15
  Presentation and diagnosis ................................................................................. 17
  Treating aneurysms ......................................................................................... 18
  Delayed neurological deterioration ............................................................... 20
  Outcome after subarachnoid hemorrhage ....................................................... 22

Acquired pituitary dysfunction ............................................................................. 24
  Symptoms and consequences of pituitary dysfunction .................................. 25
  Pituitary dysfunction after subarachnoid hemorrhage ................................ 26
  Evaluating hypothalamic-pituitary dysfunction ........................................... 26

Aims .......................................................................................................................... 29

Methods .................................................................................................................. 31

Paper I - III ............................................................................................................ 31
  Patient eligibility and ethical approval .......................................................... 31
  Acute SAH management .................................................................................. 31
  Follow-up protocol ......................................................................................... 32
  Assessment of pituitary function .................................................................. 32
  Radiological evaluation .................................................................................. 33
  Quality of life assessment .............................................................................. 33
  Statistical analyses .......................................................................................... 34

Paper IV ................................................................................................................. 35
  Clinical material and ethical approval .......................................................... 35
  Long-term follow-up evaluation ..................................................................... 36
  Statistical analysis ............................................................................................ 36

Results ...................................................................................................................... 37

Paper I - III ............................................................................................................ 37
Study population .............................................................. 37
Functional outcome ......................................................... 39
Endocrine abnormalities .................................................. 39
MRI lesions ........................................................................ 43
Quality of life ...................................................................... 43
Association between PD and general well-being ................. 44
Paper IV
Study population .............................................................. 46
Sleeping disturbances ....................................................... 48
Working capacity ............................................................... 48
Quality of Life Scale .......................................................... 48
Psychological General Well-Being .................................... 48
Reintegration to Normal Living .......................................... 49
Discussion ......................................................................... 53
Pituitary dysfunction after SAH .......................................... 53
Central hypoadrenalism ..................................................... 53
Growth hormone deficiency .............................................. 54
Hypogonadism .................................................................. 55
Thyrotropic deficiency ..................................................... 55
Prolactin ............................................................................ 56
Antidiuretic hormone ....................................................... 56
Development over time ...................................................... 56
Relation to SAH characteristics ......................................... 56
Pituitary dysfunction and outcome after SAH ..................... 57
Implications for QoL .......................................................... 57
Other implications for outcome after SAH ......................... 59
Long-term follow-up after SAH .......................................... 60
Conclusions ....................................................................... 63
Populärvetenskaplig sammanfattning ................................ 65
Acknowledgements ............................................................ 67
References ......................................................................... 69
Original papers


IV. Long-term (>20 years) Reintegration and Quality of Life after Subarachnoid Hemorrhage with Good Neurological Outcome. Sonesson B, Kronvall E, Säveland H, Brandt L, Nilsson OG. *Manuscript.*
## Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACoA</td>
<td>Anterior communicating artery</td>
</tr>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>ADH</td>
<td>Antidiuretic hormone</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computerized tomography</td>
</tr>
<tr>
<td>DCI</td>
<td>Delayed cerebral ischemia</td>
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<tr>
<td>FSH</td>
<td>Follicle-stimulating hormone</td>
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<tr>
<td>GH</td>
<td>Growth hormone</td>
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<tr>
<td>GHD</td>
<td>Growth hormone deficiency</td>
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<td>GHRH</td>
<td>Growth hormone releasing hormone</td>
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<tr>
<td>GOS</td>
<td>Glasgow Outcome Scale</td>
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<tr>
<td>ICA</td>
<td>Internal carotid artery</td>
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<tr>
<td>IGF-1</td>
<td>Insulin-like growth factor 1</td>
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<tr>
<td>ITT</td>
<td>Insulin tolerance test</td>
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<tr>
<td>LH</td>
<td>Luteinizing hormone</td>
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<tr>
<td>MCA</td>
<td>Middle cerebral artery</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>PD</td>
<td>Pituitary dysfunction</td>
</tr>
<tr>
<td>PGWB</td>
<td>Psychological General Well-Being</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>QOLS</td>
<td>Quality of Life Scale</td>
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<tr>
<td>RNL</td>
<td>Reintegration to Normal Living</td>
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<tr>
<td>SAH</td>
<td>Subarachnoid hemorrhage</td>
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<tr>
<td>SHBG</td>
<td>Sex hormone-binding globulin</td>
</tr>
<tr>
<td>SIADH</td>
<td>Syndrome of inappropriate ADH secretion</td>
</tr>
<tr>
<td>SST</td>
<td>Short Synacthen test</td>
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<tr>
<td>T&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Triiodothyronine</td>
</tr>
<tr>
<td>T&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Thyroxine</td>
</tr>
<tr>
<td>TBI</td>
<td>Traumatic brain injury</td>
</tr>
<tr>
<td>TCD</td>
<td>Transcranial Doppler</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid-stimulating hormone</td>
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Background

Subarachnoid hemorrhage

Spontaneous subarachnoid hemorrhage (SAH), non-traumatic bleeding into the space confined by the pial and arachnoid membranes, which surround the brain and spinal cord, is caused by a ruptured cerebral aneurysm in 85% of cases. If aneurysmal origin can be excluded the cause will usually stay unknown. Despite state-of-the-art treatment efforts, aneurysmal SAH remains an extremely severe condition; the risk of dying within a month after hemorrhage is over 30%. Survival is many times at the cost of functional impairments, mood disorders, sleeping disturbances, fatigue and reduced quality of life (QoL).

Historical perspective and epidemiology

The pathophysiological basis of aneurysmal SAH, its complications and its consequences, makes up an intricate jigsaw puzzle that has been assembled over many centuries and in which the last pieces are yet to be laid.

The anatomical dissertation of English physician William Harvey, Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus, published in 1628, formed the foundation for the modern understanding of the blood circulation with the concept of arteries distinguished from venous vessels. Only a few decades later, in 1664, Harvey’s compatriot and colleague Thomas Willis wrote Cerebri Anatomie: Cui Accesisit Nervorum Descriptio et Usus, a comprehensive treatise on the anatomy of the central nervous system. Illustrated by fellow scientist and architect Christopher Wren (whose tour de force as architect was Saint Paul’s cathedral in London), the book contains the description of the cerebral vasculature including the anastomotic arterial circle with supply from both carotid and vertebral arteries that now bears Willis’s name (Figure 1). Possibly, the discovery of collateral circulation to the brain was inspired by the successful resuscitation of Anne Greene, a housemaid sentenced to death by hanging in 1650.
Taking the step from anatomy and physiology to pathology, Roman physician Giovanni Maria Lancisi was the first to describe the abnormal arterial dilations that constitute aneurysms. His findings were posthumously published in 1728, a century after Harvey’s “De Motu Cordis”. Subsequently, Giovanni Morgagni of Padua is generally credited with the first description of a cerebral aneurysm in 1761, and Franz Biumi of Milan with the first report of SAH from a ruptured aneurysm in 1765.5,6

Another step further, from pathology to clinical medicine, was taken during the 19th century. In 1859, William Gull presented a collection of autopsy findings in 62 cases of ruptured and unruptured cerebral aneurysms with accurate descriptions of the symptoms associated with rupture and the distinction between asymptomatic aneurysms, aneurysms presenting with rupture and aneurysms causing symptoms by compressing adjacent nerve tissue.7 A 19th century case of importance for Swedish political history was Crown Prince Karl August, who died suddenly while inspecting troops in 1810. In a retrospective review of the circumstances, including the post-mortem examination, Erik Ask-Upmark and David Ingvar found it beyond doubt that the heir apparent died from SAH.8 The incident had profound consequences, with ensuing political turmoil resulting in, among other things, the importing of French Napoleonic war veteran Jean-Baptiste Bernadotte to take place as monarch, producing the royal dynasty that continues to this day.

From the days of Lancisi up to the first decades of the 20th century, cerebral aneurysms were most commonly thought to represent syphilitic lesions.9 While this etiology has become a rarity, other lifestyle-related risk factors for aneurysmal SAH have emerged, such as hypertension, cigarette smoking and excessive alcohol
According to present day epidemiological studies, the worldwide incidence of spontaneous/aneurysmal SAH is 9 per 100,000 and year. The risk of SAH increases with age, although half of those afflicted are <55 years of age. The risk is also higher in females and persons with Japanese or Finnish ethnicity. Hereditable disorders associated with formation of intracranial aneurysms include Ehlers-Danlos syndrome, Marfan’s syndrome and polycystic kidney disease.

**Presentation and diagnosis**

As described by Gull in 1859, the typical presentation of SAH is intense headache with sudden onset. There may be loss of consciousness, which can be transient. However, on hospital admission, the majority of patients have a reduced level of consciousness, The most severe bleedings result in *mort subita*. Nuchal rigidity, nausea and vomiting are also common symptoms. Focal neurological deficits are typically seen in patients with hemorrhage extending into the brain parenchyma. Clinical status on hospital admission is graded according to Hunt and Hess (Table 1) or the World Federation of Neurological Surgeons. These grading scales take into account the patient’s level of consciousness and are helpful in determining the clinical severity of the bleed, which is the most important indicator for prognosis.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>I</td>
<td>Asymptomatic or mild headache and slight nuchal rigidity</td>
</tr>
<tr>
<td>II</td>
<td>Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy</td>
</tr>
<tr>
<td>III</td>
<td>Drowsiness, confusion or mild focal neurologic deficit</td>
</tr>
<tr>
<td>IV</td>
<td>Stupor, moderate-severe hemiparesis, possibly early decerebrate rigidity</td>
</tr>
<tr>
<td>V</td>
<td>Deep coma, decerebrate rigidity, moribund appearance</td>
</tr>
</tbody>
</table>

Ophthalmological symptoms and signs include diplopia from 3rd, 4th and 6th cranial nerve palsies. Fundoscopy may reveal retinal or preretinal hemorrhage, Terson’s syndrome. The diagnosis of SAH in living subjects long relied on analysis of cerebrospinal fluid (CSF), usually acquired by a lumbar spinal tap. Non-invasive diagnosis was made possible with computerized tomography (CT) in the mid 1970’s. Diagnosis by CT has been helpful in showing the distribution of the extravasated blood to give a hint of the location of a ruptured aneurysm, and to demonstrate hydrocephalus, intraventricular or intracerebral hematomas. Quantification of the extent of bleeding on CT can also prognosticate outcome. The classic grading system by Fisher et al (Table 2) was devised to assess the risk of cerebral vasospasm, which is discussed later.
In 1927, Portuguese neurologist Egas Moniz described the technique of cerebral angiography\textsuperscript{26}, enabling depiction of the cerebral vasculature in living subjects, thus paving the way for the diagnosis and treatment of cerebrovascular abnormalities. In the specific case of a patient presenting with SAH, the angiographic examination is performed with the aim of detecting the origin of the bleed, usually an aneurysm. (Moniz was to be awarded the 1949 Nobel Prize for physiology or medicine, by irony of fate not for the imaging technique that continue to benefit great numbers of patients with cerebrovascular disorders, but for the technique of prefrontal leucotomy for psychosis, which eventually has come into disrepute.)

Over the years, new angiographic techniques have been developed and refined. CT angiography with intravenous contrast administration has emerged as a less invasive alternative to catheter angiography, but may be insufficient in detecting small lesions.\textsuperscript{27} However, technical advances have improved image quality.\textsuperscript{28} To date, 3-dimensional rotational digital subtraction angiography is the most accurate technique for detecting and describing the morphology of cerebral aneurysms (Figure 2).

**Figure 2.** Radiological modalities: (A) CT showing subarachnoid hemorrhage, (B) CT angiography showing an anterior communicating artery aneurysm and (C) 3-dimensional digital subtraction angiography showing the same aneurysm in better resolution.

### Treating aneurysms

While the annual rupture risk of most accidentally found cerebral aneurysms is low,\textsuperscript{29,30} a ruptured aneurysm is prone to rebleed. The risk has been estimated to 4%
during the first 24 hours, 1-2% per day during the first 2 weeks and 50% during the first 6 months. A second bleeding is usually more severe than the first, and more likely to cause poor outcome. Therefore, ruptured aneurysms call for prompt and permanent occlusion, which is done in all but the most desolate cases. The first successful ligation of the neck of a cerebral aneurysm by means of a hemostatic clip was performed by Walter Dandy in 1937. Clipping (Figure 3) was to replace surgical wrapping and Hunterian ligation as the principal way of preventing rebleeds, and remained so for many decades. The method was refined with the introduction of the surgical microscope to neurovascular surgery and improvements in aneurysm clip design by prominent neurosurgeons such as Herbert Olivecrona, who introduced blades that could be reopened for readjustment, and Frank Mayfield, with blades closing with a miniature spring action mechanism and serrated inner surfaces to avoid slipping.

![Figure 3. Clipping. A left-sided posterior communicating artery aneurysm compressing the oculomotor nerve (arrow), before (A) and after occlusion with a Yaşargil clip (B).](image)

The 1980’s and 1990’s saw the advent of endovascular techniques in treating cerebrovascular pathologies, with the introduction of Guglielmi detachable coils specifically for occluding aneurysms in 1991 (Figure 4). This has over the last years become the method of choice for securing ruptured aneurysms in many centers and advocated as such in several guidelines. Clipping, however, is still preferred with broad-based aneurysms, especially in the middle cerebral artery (MCA) bifurcation, and in the presence of a space-occupying parenchymal hematoma that needs to be evacuated. As a first step measure, before permanent aneurysm occlusion, antifibrinolytics, such as tranexamic acid, has been shown to reduce the risk of early rebleeds. Blood pressure control has also been recommended as a measure to prevent aneurysm re-rupture.
Figure 4. Coiling. An anterior communicating artery aneurysm (arrow), before (A) and after (B) occlusion with coils.

Delayed neurological deterioration

During the first weeks after ictus, SAH patients are at risk of developing delayed neurological deterioration. Common intracranial causes of such deterioration are aneurysm rebleeds, hydrocephalus and delayed cerebral ischemia (DCI); systemic causes include hyponatremia, hyperthermia, hyperglycemia, hypercapnia and cardiopulmonary complications such as pulmonary edema and takotsubo cardiomyopathy. The management of hydrocephalus, hyponatremia and DCI after SAH requires specific considerations and are discussed in more detail.

Acute hydrocephalus after SAH is caused by obstruction of CSF spaces and arachnoid villi by the hemorrhage and is treated by CSF drainage, either via an external ventricular drain or a lumbar drain. The insertion of a ventriculostomy catheter has the advantage of enabling measurement of intracranial pressure, as described by Lundberg in 1960. This is especially important in unconscious or sedated patients.

Clinically significant hyponatremia (<130 mmol/L) is seen in 20% of patients. The cause of hyponatremia following SAH is usually attributed to either syndrome of inappropriate ADH secretion (SIADH) or cerebral salt wasting. Treatment for hyponatremia in the acute phase following SAH usually consists of sodium replacement, as fluid restriction is potentially harmful in patients who are at risk for vasospasm. Fludrocortison and tolvaptan are treatment options when substitution is insufficient to restore sodium concentrations to normal.

Delayed cerebral ischemia following aneurysmal SAH remains a poorly understood complication. Although potentially preventable, it is many times frustratingly difficult to manage. The clinical diagnosis is defined as the onset of a neurological deficit or decrease in the level of consciousness, lasting for at least one hour and which can be not attributed to any other specific cause. Such symptoms are seen in about 30% of cases, and may lead to permanent neurological sequelae,
which is reflected in that DCI doubles the risk of poor neurological outcome.\textsuperscript{51} Permanent ischemic brain injury is not always symptomatic, silent cerebral infarctions make up 20\% of DCI events.\textsuperscript{52} The cause is multifactorial; cerebral vasospasm seen on angiography is doubtlessly involved, other possible contributing factors include microcirculatory vasospasm,\textsuperscript{53} microthrombosis\textsuperscript{54} and cortical spreading depression.\textsuperscript{55}

Cerebral vasospasm evident on angiography following SAH (Figure 5) was first demonstrated in 1951 by Ecker and Riemenschneider.\textsuperscript{56} This coincides with typical time-frame of DCI, 3-14 days after SAH, and has been postulated to be the main contributing factor.\textsuperscript{50} Non-invasive monitoring of vasospasm can be achieved by means of ultrasonic examinations, transcranial Doppler (TCD), which enables measurements of blood flow velocities in the main cerebral arteries. Elevated velocities $>120$ cm/s in the MCA have been correlated to angiographic vasospasm.\textsuperscript{57,58} Conversely, low blood flow velocities have been found to predict absence of vasospasm.\textsuperscript{59}

![Figure 5. Cerebral vasospasm with resulting delayed cerebral ischemia. Digital subtraction angiography within 24 hours of clinical presentation (A) and after 5 days (B). On the later examination, arterial narrowing is seen in the proximal middle cerebral artery and in the anterior cerebral artery (ACA) (arrows). A follow-up MRI (C) reveals infarctions in areas with blood supply from the ACA.](image)

Management of DCI includes prophylactic administration of nimodipine, which has been shown to reduce the risk of ischemic deterioration and poor outcome.\textsuperscript{60} Hypovolemia, hypotension, anemia and hypoxia should be avoided in order not to compromise cerebral blood flow and cerebral oxygenation.\textsuperscript{44} With clinical suspicion of DCI, induced hypertension is recommended.\textsuperscript{43} When there is a correlation between ischemic symptoms and angiographic vasospasm, endovascular angioplasty should be considered.\textsuperscript{18}

After the initial weeks of instability with risk for secondary effects from the bleed, there is usually a transition into a less dramatic course of recovery and rehabilitation.
Outcome after subarachnoid hemorrhage

Aneurysmal SAH carries high case fatality, 32% within 28 days in a population-based study, but rates are decreasing. Improved medical management is likely a contributing factor to this decline. However, the recovery for the increasing proportion of survivors is often adversely influenced by neurological, cognitive or psychological sequelae. The prognosis after SAH of unknown cause has been considered benign, but this group of patients may also suffer similar consequences.

Functional outcome: Whether the result of focal neurological deficits, cognitive impairments or behavioral changes, or a combination of the three, functional outcome reflects the individual's ability to regain the capacity to handle the tasks and responsibilities of daily living. The Glasgow Outcome Scale (GOS), originally devised in 1975 as a generic scale to grade outcome after severe brain damage, became the WFNS's official tool to classify outcome after SAH in 1987. The scale consists of five steps, from death to good recovery, separated by three levels of disability (Table 3). The scale is often dichotomized into unfavorable outcome (death, vegetative state and severe disability) and favorable outcome (moderate disability and good recovery), the latter roughly corresponding to independence in the activities of daily living. Clinical variables that predict unfavorable outcome include increasing age, worse admission status, greater SAH thickness on CT, larger size and posterior circulation locale of the ruptured aneurysm, intraventricular hemorrhage and intracerebral hematoma. Alternative, but similar scales for grading functional outcome include the Barthel index, the modified Rankin scale and the extended GOS. Reintegration to Normal Living (RNL), which examines functional recovery with emphasis on psychosocial aspects, has also been used in the evaluation of SAH patients.

Table 3. Neurological outcome according to the Glasgow Outcome Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>1</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>Vegetative state</td>
</tr>
<tr>
<td>3</td>
<td>Severe disability</td>
</tr>
<tr>
<td>4</td>
<td>Moderate disability</td>
</tr>
<tr>
<td>5</td>
<td>Good recovery</td>
</tr>
</tbody>
</table>

Subtle functional impairments resulting from cognitive defects can be disabling, also in patients with favorable outcome according to GOS. Such defects have been defined in terms of impaired memory, perception, executive function and language. Focal encephalomalacia seen on MRI in patients with surgically treated aneurysms has been associated with poorer cognitive outcome, as has...
hippocampal volume loss regardless of aneurysm treatment modality. Ventricular enlargement following SAH can indicate cerebral atrophy and is correlated with cognitive deficits. Ventriculomegaly may also be caused by chronic post-hemorrhagic hydrocephalus, with functional impairments reversible with implantation of a CSF shunt.

Ability to return to work is a crucial aspect of functional recovery for many individuals. As a measure for recovery after SAH it has limitations, many patients may already have reached retirement from their professional careers. Also, factors unrelated to the SAH may be of importance for return to previous employment. The frequency of inability to return to work for SAH survivors has been reported to be in the range of 27% to 57%. However, these studies have mostly included patients with favorable functional outcome.

Psychiatric disorders: Mood disorders are not uncommon after SAH and have impact on recovery. Depression has been diagnosed in 9% to 23% using the the Hospital Anxiety and Depression Scale, in 10% to 28% using the Beck Depression Index, in 21% using the Montgomery Åsberg Depression Rating Scale, and in 36% using the Zung Self-rating Depression Scale. Anxiety is also common after SAH. As assessed by the Hospital Anxiety and Depression Scale, it has been reported in 11% to 59% of SAH patients. Post-traumatic stress disorder in both SAH survivors and their significant others has been identified as a treatable cause for psychosocial disability.

Fatigue and sleeping disturbances: Fatigue, a feeling of exhaustion that is not caused by physical effort and not relieved by rest, is a common problem after SAH. Its etiology is not clear, but it is also seen with other stroke subtypes and represents a disabling problem and therapeutic challenge. Sleeping disorders are also often encountered in SAH patients. Both initiating and maintaining sleep are commonly reported problems, and may contribute to daytime fatigue.

Quality of life: The concept of QoL deals with the individual’s self-perceived well-being or lack thereof. The term health-related QoL is often used when the concept is discussed in conjunction with disease. Measures for health-related QoL typically include dimensions such as subjective health status, disability and pain, along with anxiety, depression and fatigue. Thus, there may be an overlap with these aspects of outcome. Reduced psychological well-being after SAH has been demonstrated in many studies. Instruments for evaluating QoL after SAH have included EQ-5D, the Nottingham Health Profile (NHP), the Short Form-36, and the Stroke Specific Quality of Life scale. Predictors for QoL outcome include clinical admission status, sex, age, surgical versus endovascular aneurysm therapy and chronic hydrocephalus. Impaired QoL after SAH has been associated with physical disability, but also in apparently well-recovered patients, associated with
sequelae such as cognitive defects, fatigue, mood disorders and sleeping disturbances.

**Long-term somatic morbidity:** In addition to the neurological, neuropsychological and psychiatric disturbances, long-term SAH survivors face excess morbidity and mortality from somatic illness. This is mainly caused by cardiovascular and cerebrovascular diseases.

**Acquired pituitary dysfunction**

The functions of the pituitary gland are fairly recent discoveries. It was long thought to represent a sort of sewer to the soul where the waste product of mental function, mucus or pituita, was secreted into the nasopharynx. The more distinguished role as the master gland of the endocrine system was recognized in the late 19th and early 20th century with the discovery of hormones as biochemical messengers between remote parts within an organism and the association between growth abnormalities, such as gigantism and acromegaly, and pituitary disease.

![Diagram of the pituitary gland](image)

**Figure 6.** Schematic representation of the pituitary gland with the hypothalamic nuclei involved in endocrine function and the vascular supply to the hypophyseal portal system, which runs through the pituitary stalk. The nuclei: ARC, arcuate; PO, preoptic; PV, paraventricular, SO, supraoptic. The arteries: IAA, infundibular arteries, IHA, inferior hypophyseal artery, SHA, superior hypophyseal artery. Adapted from Besser and Thorner.

Secretion of pituitary hormones is governed by release of stimulating factors, hormone-releasing hormones, and inhibitory factors from the hypothalamus. Anatomically, the hypothalamus is vascularized by branches from the ICA. The superior hypophyseal artery enters the hypothalamus at the median eminence,
between the infundibulum and tuber cinereum, where it anastomoses with the infundibular arteries from the posterior communicating artery and forms a portal system (Figure 6).\(^\text{111}\) Releasing hormones are secreted into the first capillary plexus and transported through the portal vein running in the pituitary stalk to the secondary plexus, which also has supply from the inferior hypophyseal artery, in the anterior lobe where they bind to receptors that activate or inhibit the release of the pituitary hormones: adrenocorticotropic hormone (ACTH) or corticotropin, growth hormone (GH) or somatotropin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH) or thyrotropin, and prolactin. The posterior lobe, or neurohypophysis, secretes oxytocin and antidiuretic hormone (ADH) directly from hypothalamic neurons with axons extending through the pituitary stalk.\(^\text{112}\)

Pituitary dysfunction (PD) may affect single or multiple endocrine axes and can result from both hypothalamic and pituitary disease. Common causes are sellar tumors, including pituitary adenomas, and pituitary apoplexy.\(^\text{113}\) The order of failure usually starts with GH followed by FSH and LH, and finally TSH and ACTH.\(^\text{114}\) Surgery for pituitary tumors can relieve but also produce dysfunction.\(^\text{115}\) Cranial irradiation is another well-established cause of PD. The severity and extent of axes affected are radiation dose dependent: the GH axis is most sensitive, followed by ACTH and TSH deficiencies.\(^\text{115}\) The deficits tend to progress over time, which may be due to secondary pituitary atrophy from lack of stimulation from hypothalamic hormone-releasing hormones or from delayed hypothalamic or pituitary radiation injury.\(^\text{116}\)

More recently, head injury has become recognized as a cause of PD.\(^\text{117}\) There have been several reports of PD following traumatic brain injury (TBI),\(^\text{118-121}\) with a frequency of up to 50%.\(^\text{122}\) Clinical TBI severity, increased intracranial pressure and number of days with artificial ventilation have been shown to be predictors for PD.\(^\text{121}\)

### Symptoms and consequences of pituitary dysfunction

Apart from the obvious symptoms, such as arrested growth in a child with growth hormone deficiency (GHD) or amenorrhea in women with hypogonadism, PD is known to produce more diffuse neuropsychological symptoms akin to those seen after SAH. Patients with corticotropin deficiency are often plagued by fatigue, weakness and altered mental activity.\(^\text{113}\) Fatigue is also seen with thyrotropin deficiency.\(^\text{113}\) Growth hormone deficiency is linked to symptoms of mental distress and cognitive dysfunction,\(^\text{123}\) and also with reduced QoL.\(^\text{124}\) In the long run, patients with hypopituitarism have shortened life expectancy, the condition is associated with an increased mortality risk, especially from vascular disorders.\(^\text{125}\)
Pituitary dysfunction after subarachnoid hemorrhage

The close anatomical relationship between the hypothalamus and pituitary stalk, and common aneurysm locations in the circle of Willis (Figure 7), makes these structures prone to injury from SAH. The jet from aneurysm rupture piercing into nerve tissue, the drop in cerebral perfusion pressure and blood flow resulting from the sudden increase in intracranial pressure, along with compression from hemorrhage in the basal cisterns and third ventricle can all be contributing factors. Secondary events such as hydrocephalus and vasospasm may also cause hypothalamic and pituitary stalk injury. These circumstances and the similarities between neuropsychological symptoms observed in PD and after SAH, has led to speculation whether PD may be a complication to SAH with impact on outcome. This speculation is supported by post-mortem findings of hypothalamic injury in SAH victims. There have been studies reporting endocrine abnormalities indicating PD after aneurysmal SAH. However, the results of these studies have been variable and conflicting, reporting the occurrence of PD from rare to common.

Figure 7. View through the operating microscope (left subfrontal approach) of the close anatomical relationship between parts of the circle of Willis (the internal carotid artery, ICA; posterior communicating artery, PCoA; and proximal anterior cerebral artery, ACA) and the pituitary stalk (PS). The optic nerve (ON) is gently retracted. The hypothalamus is obscured by the optic tract (OT).

Evaluating hypothalamic-pituitary dysfunction

Corticotropin deficiency: Secretion of ACTH is mainly stimulated by corticotropin-releasing hormone (CRH) from the paraventricular nuclei in the hypothalamus. ACTH, in turn, stimulates production and release of cortisol from the adrenal cortex. This is known as the hypothalamic-pituitary-adrenal axis. Hypothalamic CRH secretion is activated as a response to stress and as a negative
feedback system, inhibited by elevated cortisol concentrations. Corticotropic
deficiency, or central hypoadrenalism, can be diagnosed indirectly by measuring basal
concentrations of cortisol.\textsuperscript{135} Sampling is performed in the morning, soon after
waking, when the circadian variation of plasma cortisol peaks. Another indirect way
of assessment is the short Synachten test (SST),\textsuperscript{136} with administration of the
synthetic ACTH analogue Synacthen, which stimulates adrenal cortisol secretion.
Estimation of central hypoadrenalism using SST is based on the presumption that
long lasting loss of ACTH stimulation leads to adrenal atrophy and ACTH receptor
downregulation.\textsuperscript{137} The gold standard for the diagnosis of central hypoadrenalism
is the insulin tolerance test (ITT),\textsuperscript{138} in which induced hypoglycemia evokes a stress
response that stimulates CRH activity. The disadvantage of the ITT pertains to the
danger of inducing hypoglycemia with risk of inducing epileptic seizures and
myocardial ischemia, and is generally considered contraindicated in patients with
these conditions and in the elderly.\textsuperscript{138,139}

**Growth hormone deficiency:** GH secretion is stimulated by growth hormone-
releasing hormone (GHRH) from the arcuate nuclei and inhibited by somatostatin
from the paraventricular nuclei. The anabolic effects of GH are mainly mediated by
insulin-like growth factor 1 (IGF-1). As GH is secreted in a pulsatile manner,
sampling is not helpful in diagnosing deficiency.\textsuperscript{140} Concentrations of IGF-1 are more
stable and can be used in screening for GHD. Direct, and more accurate ways of
examining pituitary capacity for GH secretion include the GHRH + arginine and the
glucagon stimulation tests. The ITT can also be used with the added advantage of
including the integrity of the hypothalamic-pituitary axis and simultaneous
assessment of ACTH deficiency.\textsuperscript{139}

**Gonadotropin deficiency:** Gonadotropin-releasing hormone (GnRH) is produced
from neurons scattered in the hypothalamus, primarily in the preoptic area, and
stimulates pituitary secretion of FSH and LH. These hormones act on the internal
genitalia, producing the sex hormones estradiol and testosterone. Central or
secondary hypogonadism is diagnosed with low estradiol or testosterone
concentrations combined with inappropriately low FSH and LH. Diagnosis is
usually based on clinical finding and supported by hormone concentrations,\textsuperscript{141} but
dynamic testing can be performed with GnRH stimulation.\textsuperscript{135}

**Thyrotropin deficiency:** TSH secretion is stimulated by thyrotropin-releasing
hormone from the paraventricular nuclei, and, in turn, stimulates triiodothyronine
(T\textsubscript{3}) and thyroxin (T\textsubscript{4}) production and secretion from the thyroid gland. Central
hypothyreosis is diagnosed when low concentrations free T\textsubscript{4} are seen with normal or
decreased TSH. With the development of highly sensitive assays for TSH, stimulation
tests are not used.\textsuperscript{141}
Prolactin: Prolactin is secreted with diurnal variation, which peaks in the early hours of the morning and decreases over the waking hours. Pituitary prolactin synthesis and release is inhibited by dopaminergic neurons in the arcuate nuclei, which means that injury to the hypothalamus or pituitary stalk results in hyperprolactinemia.

Antidiuretic hormone: Vasopressin or ADH is produced in the paraventricular and supraoptic nuclei and transported via axons for storage in the posterior pituitary lobe. Secretion is stimulated by increased plasma osmolality and regulates balance of extracellular fluid and sodium concentrations through renal water resorption. Acute hypothalamic or pituitary compromise can cause uncontrolled ADH release, syndrome of inappropriate ADH secretion (SIADH), which results in water retention and hyponatremia. Chronic ADH deficiency results in diabetes insipidus, with polyuria, thirst polydipsia and hypernatremia if not compensated. Dynamic evaluation of ADH secretion and ability for urine concentration can be achieved with the water deprivation test.19
Aims

The subject of this dissertation is spontaneous SAH and the many times dire consequences of this affliction. Focus lies on endocrine dysfunction in the aftermath of SAH and on QoL and reintegration following SAH. The specific aims of the studies that constitute the thesis were:

• to investigate the prevalence of endocrine abnormalities of pituitary and hypothalamic origin longitudinally in a 2-year perspective following aneurysmal SAH (paper I and II),

• to investigate outcome in terms of psychological well-being in the same cohort of patients and during the same period of time (paper III),

• to examine the relationship between disturbed pituitary function and health-related QoL (paper III)

• to investigate outcome after spontaneous SAH in a separate cohort in a time perspective of over 20 years in terms of reintegration and QoL (paper IV).
Methods

Paper I - III

Patient eligibility and ethical approval

Patients with acute aneurysmal SAH admitted to the Department of Neurosurgery at the University Hospital in Lund were prospectively recruited for study participation from October 2006 until April 2010. Patients over 18 years of age who could be subjected to hormonal blood sampling within 5 to 10 days after ictus were eligible for inclusion. The study protocol was approved by the Regional Ethical Review Board in Lund (65/2006) and registered at the ClinicalTrials.gov database (NCT01101711).

Acute SAH management

After diagnosis of SAH with suspicion of aneurysmal origin, patients were transferred from local hospitals to the neuro-intensive care unit at our department without delay. Clinical status on admission was graded according to Hunt and Hess (Table 1). The distribution of blood in the subarachnoid cisterns seen on CT was graded according to Fisher (Table 2). Tranexamic acid was administered to prevent early rebleeds prior to permanent aneurysm occlusion. A ventriculostomy catheter was placed in unconscious patients for monitoring intracranial pressure and to drain cerebrospinal fluid (CSF) in cases of acute hydrocephalus. Ruptured aneurysms were permanently secured by coiling or clipping within 24 hours after hospital admission. During the first 10–14 days after ictus, nimodipine was administered orally to prevent DCI. Fluid and electrolyte balance was monitored and patients were kept euvoletic to slightly hypervolemic. Clinically significant hyponatremia was treated. Neurological status was closely monitored as to detect signs of deterioration. Daily measurements of blood flow velocities in the middle cerebral (MCA) and anterior cerebral arteries using transcranial Doppler (TCD) were performed to screen for vasospasm. In cases of severe or symptomatic vasospasm, angioplasty either with intra-arterial pharmacological agents, such as nimodipine or verapamil, or balloon dilatation was performed.
Follow-up protocol

Patients were evaluated during the acute phase after SAH and at 3 follow-up occasions; after 3-6 months, after 6-12 months and after 12-24 months. The evaluation included neurological outcome according to GOS (Table 3) and assessment of pituitary function. Health-related QoL was assessed at the follow-up visits. The study protocol also included a follow-up brain MRI examination.

Assessment of pituitary function

Comprehensive assessments of pituitary function were performed. Basal hormone concentrations were examined along with electrolytes and osmolality at all 4 time-points. The battery of tests included blood samples for morning (9.00 am) plasma levels of FSH, LH, estradiol (in women), testosterone (in men), SHBG, TSH, T₄, ACTH, cortisol, prolactin, Na, K; serum levels of GH and IGF-1, and serum and urine osmolality. Local reference values were used with a graded interpretation of morning cortisol concentrations adapted after Courtney et al and Grossman (Table 4).

Table 4. Interpretation of basal cortisol concentrations

<table>
<thead>
<tr>
<th>Concentration range (nmol/L)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-Cortisol</td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>Deficiency</td>
</tr>
<tr>
<td>100-249</td>
<td>Probable deficiency</td>
</tr>
<tr>
<td>250-450</td>
<td>Probable normal function</td>
</tr>
<tr>
<td>&gt;450</td>
<td>Normal function</td>
</tr>
</tbody>
</table>

In addition to the evaluation by basal concentrations, dynamic tests were used to assess somatotropic function at follow-up after 3-6 months, and both somatotropic and adrenocorticotropic function after 12-24 months.

For assessment of adrenocorticotropic function, an ITT was performed at the 12-24 months follow-up. In response to induced hypoglycemia, cortisol concentrations <500 nmol/L indicated central hypoadrenalism. Contraindications to ITT were age >65 years, diabetes mellitus and epilepsy. These patients were subjected to the SST, in response to which cortisol concentrations <550 nmol indicated hypoadrenalism.

For assessment of somatotropic function, the GHRH-arginine stimulation test was performed at 3-6 months and the ITT at 12-24 months. When the ITT was contraindicated, the GHRH-arginine stimulation test was repeated. Peak concentrations of GH <3µg/L in response to the hypoglycemia induced during the ITT indicated GHD. Peak concentrations of GH after GHRH-arginine stimulation were interpreted in relation to body mass index (BMI). In patients with BMI >25
kg/m², the cut-off for GHD was <11 µg/L; in patients with BMI 25-30 kg/m², <8 µg/l; and in patients with BMI >30 kg/m², <4 µg/L.

**Radiological evaluation**

As a part of our clinical routine for aneurysmal SAH patients, a follow-up brain MRI examination was performed. Lesions from infarcts and hemorrhage using T2 fluid attenuated inversion recovery transverse, T2 turbo spin echo transverse and T2 turbo spin echo sagittal sequences. The assessments were performed blinded to the other outcome measures. The extent of MRI lesions was scored based on size and number; 0 for no lesions, 1 for 1-2 lesions ≤1cm in largest diameter, 2 for lesions >1cm or numbering ≥3 for the following anatomical territories: right or left frontal lobe, right or left temporal lobe, right or left parietal lobe, right or left occipital lobe, right or left central area, brainstem and cerebellum. Right or left hypothalamic lesions were given a score of 1 if present, making up a total lesion score of 0-26 (Figure 8). Presence of hydrocephalus was also noted.

![Figure 8](image)

> Figure 8. Examples of MRI lesions scores. A 2 points for a right frontal lesion (*) + 1 point for a right central lesion (arrow) = 3 points. B 2 points for multiple left frontal lesions (*) + 1 points for a left hypothalamic lesion (arrow) = 3 points.

**Quality of life assessment**

Health-related QoL was assessed using the Psychological General Well-being (PGWB) questionnaire. Responses to 22 multiple-choice questions were graded 1 to 6, giving a total score of *general well-being* of 22-132. The questions are also divided into 6 dimension subscales; *anxiety, depressed mood, sense of positive well-being,*
self control, general health and vitality. Higher scores reflect more positive responses, also in the subscales anxiety and depressed mood (Table 5). Data on PGWB scores from 2162 randomly selected inhabitants of the city of Malmö (located within our catchment area), served as reference. Mean reference scores are listed in Table 5.

<table>
<thead>
<tr>
<th></th>
<th>Possible range</th>
<th>Reference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General well-being (total score)</td>
<td>22-132</td>
<td>102.9 (102.1-103.8)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5-30</td>
<td>24.1 (23.9-24.3)</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>3-18</td>
<td>15.5 (15.4-15.7)</td>
</tr>
<tr>
<td>Sense of positive well-being</td>
<td>4-24</td>
<td>16.1 (16.0-16.3)</td>
</tr>
<tr>
<td>Self control</td>
<td>3-18</td>
<td>15.3 (15.2-15.4)</td>
</tr>
<tr>
<td>General health</td>
<td>3-18</td>
<td>14.6 (14.5-14.8)</td>
</tr>
<tr>
<td>Vitality</td>
<td>4-24</td>
<td>17.2 (17.0-17.4)</td>
</tr>
</tbody>
</table>

CI, confidence interval

**Statistical analyses**

The statistical analyses were performed using IBM SPSS statistics v. 20 and v. 22 (IBM Corporation, Armonk, NY).

The Mann–Whitney U test was used to compare age, Hunt and Hess grade, Fisher grade and GOS in patients with evidence of PD versus those with normal pituitary function. Fisher’s exact test was used for similar comparisons of binary outcome parameters: sex, aneurysm location (circle of Willis versus other), treatment modality (clipping versus coiling), external ventricular drainage (acute hydrocephalus), shunt placement (chronic hydrocephalus), DCI and TCD blood flow velocities >120 cm/s.

Univariate and multivariate linear regression models were used to examine variables associated with total PGWB scores. The models incorporated age, sex, Hunt & Hess grade, aneurysm treatment modality (clipping or coiling), delayed cerebral ischemia, shunting for hydrocephalus, MRI lesion score and PD. Subsequently, two-way analysis of variance (ANOVA) was performed for more detailed examination of the effect of PD, including the two most commonly affected individual endocrine axes central hypoadrenalism and GHD, and the effect of time, on general well-being scores. One-sided independent samples t-tests were used for post-hoc comparisons of mean scores at individual time-points.

To specifically examine whether resolved or new onset PD between two follow-up occasions was associated with worsened or improved QoL, mean changes of total PGWB scores in these groups were compared to those with unchanged endocrine status using one-way ANOVA.
Spearman rank correlations were calculated for the relationship between MRI lesion scores and GOS scores. Probability values of < .05 were considered statistically significant.

Paper IV

Clinical material and ethical approval

Between 1977 and 1984, 567 patients with aneurysmal SAH and 101 with SAH of unknown cause (negative angiogram) were admitted to the Department of Neurosurgery in Lund. Of these, 93 patients with aneurysmal SAH and 20 patients with SAH of unknown cause having good neurological recovery (GOS 5), were randomly selected for neuropsychological assessment and evaluation of adaptation and reintegration in the years after ictus. The results of these initial evaluations were published in 1985, 146 1986, 145 1987, 145 and 1989. 65 All patients selected for study inclusion with aneurysmal SAH were in Hunt and Hess grade I-III on hospital admission, and operated on with clip ligation of the ruptured aneurysm. All aneurysms were located in the anterior circulation. The present whereabouts of the 113 patients selected for psychological evaluation was given by the National Population Registry. Mortality data was obtained from the Swedish National Board of Health and Welfare. The survivors were contacted and questionnaires (see below) were sent out by mail. Seventy-one survivors gave their consent to participation and were included in the study. The study protocol was approved by the Regional Ethical Review Board in Lund (2004/167).

Long-term follow-up evaluation

Health-related QoL and reintegration after SAH was evaluated by self-assessment questionnaires. In addition, information was collected with respect to sleeping disturbances and general working capacity.

Quality of Life Scale (QOLS): This scale covers material circumstances, physical fitness, relationship to significant others, participation in social activities, learning, creativity, leisure activities and functional independence. 147, 148 The QOLS has been used to assess QoL after heart surgery, 149 after orthopedic trauma, 150 in fibromyalgia 151 and mild cognitive impairment. 152 The scale in the version used here consists of 16 items, scored 1-7, giving the total score a range from 16 to 112. Higher scores indicate better QoL. The average total score for healthy populations is about 90. 147
Psychological General Well-Being (PGWB): This measure for assessment of health-related QoL is described in detail above and is summarized in Table 5.

Reintegration to Normal Living (RNL): This instrument evaluates reintegration in terms of recreation, social activities, participation in the community and interaction with family and other significant persons. It has been used to assess reintegration after spinal cord injury, traumatic brain injury, stroke, and up to 5 years after aneurysmal SAH. The RNL scale consists of 11 declarative statements with a positive syntax and the subject may agree or disagree with these statements along a 10-point axis. The RNL scores are converted to an index with a 100 scale according to the formula: sum of scores/theoretical maximum sum of scores x 100: the higher the index the better the readjustment and reintegration. An index of 100 is considered to reflect full reintegration; an index between 60 and 99, mild to moderate problems of readjustment, and an index of 59 or lower, severe problems. A supplementary 17-item scale was devised in the manner of the RNL purporting to yield information with respect to psychological problem areas specifically encountered following SAH. Each item was similarly scored 1-10. Since the syntax of these latter statements is negative, scores were reversed in the analysis, i.e. the higher the score, the better the outcome and greater the disagreement with the proposed impairment. In the analysis, these items dealing with energy resources, cognition and problem solving, concentration, efficiency, mood and effect, were considered separately.

Statistical analysis

All statistical analyses were performed using SPSS v. 20 and v. 22 (IBM Corporation, Armonk, New York). Univariate and multivariate linear regression models were used to examine variables associated with QOLS and PGWB scores. The variables included were: aneurysmal origin of SAH, sex, age at SAH, age at follow-up, sleeping disturbances and ability to return to work after SAH. A factor analysis (Varimax with Kaiser Normalization) was used to examine the original and supplementary RNL items in order to elucidate underlying factors that would possibly be mutual to both the original and supplementary scale. Probability values < .05 were considered statistically significant.
Results

Paper I - III

Study population

Sixty patients with acute aneurysmal SAH were screened for study inclusion. Two from whom informed consent could not be obtained were excluded along with 7 who declined participation, leaving 51 to be included for acute phase evaluation. The study protocol comprised 3 follow-up visits, the first at 3-6 months (n=45) after the bleed, the second after 6-12 months (n=44), and the third after 12-24 months (n=44) (Figure 9). Four had previous treatment for depression and 2 had replacement therapy for primary hypothyroidism.

![Flowchart of Study Population](image_url)

All patients were in Hunt and Hess grade I-IV at hospital admission after having suffered SAH. Hemorrhage was visible on CT (Fisher grade 2 - 4) in all cases. Presence of an aneurysm was confirmed by CT or catheter angiography in all cases.
Aneurysms were located in the circle of Willis (anterior communicating artery, ICA or basilar artery apex) in close proximity of the hypothalamus and the pituitary stalk in 78% of patients (Figure 1). Other locations were MCA bifurcation (16%) and pericallosal artery (6%). All ruptured aneurysms were occluded by endovascular coiling (75%) or surgical clipping (25%). Hydrocephalus in the early phase, requiring external ventricular drainage, was seen in 13 patients (25%). Need for long-term CSF drainage requiring a ventriculoperitoneal shunt occurred in nine (18%). Neurological deterioration due to DCI was seen in 10 cases (20%). In 17 patients (33%), TCD detected blood flow velocities in MCA over 120 cm/s suggesting vasospasm. Endovascular angioplasty was performed in six patients with symptomatic cerebral vasospasm (Table 6).

Table 6. Baseline data and clinical events related to SAH for the study subjects in Paper I-III

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>55 (28-75)</td>
</tr>
<tr>
<td>Female sex</td>
<td>43 (84%)</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
</tr>
<tr>
<td>Circle of Willis (ACoA, ICA and Basilar apex)</td>
<td>40 (78%)</td>
</tr>
<tr>
<td>Other (MCA and pericallosal)</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>Hunt &amp; Hess grade</td>
<td></td>
</tr>
<tr>
<td>1: Asymptomatic/mild headache</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>2: Moderate/severe headache</td>
<td>21 (41%)</td>
</tr>
<tr>
<td>3: Drowsiness/confusion</td>
<td>17 (33%)</td>
</tr>
<tr>
<td>4: Stupor</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>5: Coma/decerebrate posturing</td>
<td>0</td>
</tr>
<tr>
<td>Fisher grade</td>
<td></td>
</tr>
<tr>
<td>1: No blood detected</td>
<td>0</td>
</tr>
<tr>
<td>2: Diffuse SAH, &lt; 1mm thick</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>3: Diffuse SAH, ≥ 1mm thick</td>
<td>28 (55%)</td>
</tr>
<tr>
<td>4: Clot in ventricle or parenchyma</td>
<td>15 (29%)</td>
</tr>
<tr>
<td>Treatment modality</td>
<td></td>
</tr>
<tr>
<td>Endovascular (coiling)</td>
<td>38 (75%)</td>
</tr>
<tr>
<td>Surgery (clipping)</td>
<td>13 (25%)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td></td>
</tr>
<tr>
<td>External ventricular drainage</td>
<td>13 (25%)</td>
</tr>
<tr>
<td>Ventriculoperitoneal shunt</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Delayed cerebral ischemia</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Vasospasm</td>
<td></td>
</tr>
<tr>
<td>TCD &gt; 120</td>
<td>17 (33%)</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>6 (12%)</td>
</tr>
</tbody>
</table>

ACoA = anterior communicating artery; ICA = internal carotid artery; MCA = middle cerebral artery; SAH = subarachnoid hemorrhage; TCD = transcranial Doppler
**Functional outcome**

Most patients had a benign clinical course; GOS scores at discharge and at the 3 follow-up occasions are summarized in **table 7**. During follow-up, all patients but 1 remaining in the study experienced favorable outcome (GOS 4-5).

**Table 7. Summary of Glasgow outcome scale (GOS) scores**

<table>
<thead>
<tr>
<th>GOS</th>
<th>Discharge (n=51)</th>
<th>3-6 months (n=45)</th>
<th>6-12 months (n=44)</th>
<th>12-24 months (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Dead</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2: Vegetative state</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3: Severe disability</td>
<td>19</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4: Moderate disability</td>
<td>30</td>
<td>17</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>5: Good recovery</td>
<td>-</td>
<td>27</td>
<td>30</td>
<td>37</td>
</tr>
</tbody>
</table>

**Endocrine abnormalities**

*Adrenal axis:* Unstimulated cortisol concentrations <250 nmol/L, indicating suspected central hypoadrenalism, were seen in 4 patients (8%) in the acute stage, in 8 patients (18%) at follow-up after 3-6 months, in 9 patients (20%) after 6-12 months and in 5 patients (11%) at 12-24 months (**Figure 10**).

![Figure 10. Frequencies of patients with evidence of hypoadrenalism at the 4 time points of assessment. Deficiency defined by basal hormone concentrations, except after 12-24 months, when dynamic tests were performed (ITT, insulin tolerance test; SST, short Synacthen test)](image-url)
Dynamic testing after 12-24 months with ITT in 30 patients resulted in cortisol concentrations <550 nmol/L in 9 patients. In 14 patients the ITT was contraindicated and the SST performed instead. This resulted in normal responses in all cases. In total, 9 of 44 (20%) of patients subjected to dynamic testing showed evidence of central hypoadrenalism (Figure 10). None of these patients had basal cortisol concentrations <250 nmol/L or >450 nmol/L at the induction of hypoglycemia.

**Somatotropic axis:** Low concentrations of IGF-1 indicating GHD were seen in six patients (12%) in the acute stage, in nine patients (20%) after 3–6 months, in 6 of 30 patients (20%) after 6-12 months and in 12 of 41 patients (29%) after 12-24 months (Figure 11).

Dynamic assessment at follow-up after 3-6 months using the GHRH-arginine stimulation test revealed 3 responses indicating GHD (7%). These three individuals all had low IGF-1 levels. At follow-up after 12-24 months, 9 of 30 patients responded to ITT with GH concentrations <3 µg/L, indicating GHD. Among those subjected to the GHRH-arginine test, 2 of 14 patients (14%) had responses indicating GHD. In total, 11 of 44 (25%) of patients subjected to dynamic testing after 12-24 months showed evidence of GHD (Figure 11). Seven of these had low IGF-1 concentrations.

**Gonadotropic axis:** The gonadotropin axis was evaluated by measuring LH and FSH levels. Estradiol was also measured in women and testosterone in relation to
SHBG levels in men. In the acute phase, 15 patients (30%; 13 female and two male) had low gonadotropin levels indicating secondary hypogonadism, but at follow up this was seen only in 2, both female. Low gonadotropin concentrations were seen in 1 female patient at 6-12 months. At 12-24 months hypogonadism was noted in 4 female patients and 1 male.

**Thyrotropic axis:** Three patients had replacement therapy for primary hypothyroidism, 2 of which were known from before inclusion to the study and 1 diagnosed during the study. Three patients (6%) had normal TSH levels in spite of low T₄ levels, indicating insufficient thyrotrophic function in the acute stage. At follow-up after 3-6 months, this was seen in one patient (2%) only and at subsequent assessments there were no abnormalities indicating thyreotropic dysfunction.

**Prolactin:** Mild hyperprolactinemia (≤35µg/L) was seen in 8 patients (16%) in the acute phase and in 1 at follow-up after 3-6 months, in 1 patient after 6-12 months and in 2 patients at 12-24 months.

**Antidiuretic hormone:** Hyponatremia requiring treatment developed in 11 patients during the acute stage. No clear distinction between cerebral salt wasting and SIADH could be made. However, at the time of sampling for study purposes there were only seven cases of mild hyponatremia (133-135 mmol/L) in the acute stage. At all 3 follow-up occasions, all patients had normal sodium levels. There were no cases of suspected diabetes insipidus.

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**Figure 12.** Frequencies of patients with evidence of pituitary dysfunction in any axis at the 4 time points of assessment
**Pituitary dysfunction of any axis over time:** Deficiencies in 1 or more axes were diagnosed in 19 (37%) patients in the acute stage, in 12 (27%) after 3-6 months (with GHD defined by dynamic tests), in 15 (34%) after 6-12 months and in 19 (43%) after 12-24 months (with GHD and hypoadrenalism defined by dynamic tests) (Figure 12). Over time, both resolution and new onset of PD was seen: between the acute stage and 3-6 months follow-up there were 5 cases of persistent PD, 11 cases of resolution and 7 cases of new onset PD; between the 3-6 and 6-12 months follow-up there were 6 cases of persistent PD, 5 cases of resolution and 6 cases of new onset PD; between the 6-12 and 12-24 follow-up there were 11 cases of persistent PD, 2 cases of resolution and 6 cases of new onset PD. Changes in individual axes are summarized in Table 8.

<table>
<thead>
<tr>
<th>ID</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A,S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>G,T</td>
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<td>N/D</td>
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<td>23</td>
<td>G</td>
<td>A</td>
<td>A,S</td>
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</tbody>
</table>

**Table 8.** Deficiencies in the different endocrine axes over time in the 46 patients that remained at follow-up. In the acute stage, 1 more patient had isolated gonadotropic deficiency and 1 had combined gonadotropic and somatotropic deficiencies. Central hypoadrenalism at 12-24 follow-up and growth hormone deficiency at 3-6 and 12-24 months follow-up were defined by dynamic tests.

<table>
<thead>
<tr>
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<th>IV</th>
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<td>35</td>
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<td>36</td>
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<td>37</td>
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<td>S</td>
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<td>39</td>
<td>A</td>
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<td>40</td>
<td>G</td>
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<tr>
<td>41</td>
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<tr>
<td>42</td>
<td>T</td>
<td>A</td>
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<td>45</td>
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</tr>
<tr>
<td>46</td>
<td>S,G</td>
<td>G</td>
<td>G</td>
<td>G</td>
</tr>
</tbody>
</table>

I, acute stage assessment; II, 3-6 months follow-up; III, 6-12 months follow-up; IV, 12-24 months follow-up; A, adrenal axis; S, somatotropic axis, G, gonadotropic axis; T, thyreotropic axis; N/D, no data
**Pituitary dysfunction in relation to clinical variables:** Patients with PD in the acute stage had significantly lower median GOS scores at discharge compared to those with normal pituitary function ($p = .018$). They were also significantly more likely to have had a ruptured aneurysm in the circle of Willis ($p = .037$) and to have their aneurysm treated by coiling ($p = .018$). At follow-up after 3-6 months, patients PD had lower median GOS scores ($p = .041$) and lower age ($p = .006$). At later time points there were no variables with statistically significant associations to PD, including age, sex, Hunt & Hess grade, aneurysm treatment modality, delayed cerebral ischemia, CSF shunting, or GOS score.

**MRI lesions**

Forty-eight patients underwent follow-up MRI examinations. Median time from SAH to examination was 3 months (range 1-11 months). With 21 patients having no visible lesions, median MRI lesion score was 1 (range 0 to 8). Frontal lesions were seen in 20 patients, temporal in 8, parietal in 4, occipital in 2, central in 9, brainstem in 1, cerebellar in 1, and hypothalamic in 6. Hydrocephalus was seen in 6 patients.

There was a statistically significant negative correlation between MRI lesion scores and GOS scores at the 3-6 months evaluation (Spearman rank correlation, $r_s = - .502$, $p = .0003$). This relationship remained statistically significant at 6-12 ($r_s = - .307$, $p = .043$) and 12-24 months ($r_s = - .348$, $p = .024$). All patients with hypothalamic MRI lesions had evidence of PD at some point in time during the study.

**Quality of life**

Scores with standard deviations are summarized in Table 9.

<table>
<thead>
<tr>
<th>Table 9. Overall Psychological General Wellbeing Index scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-6 months (n=45) Mean (SD)</td>
</tr>
<tr>
<td>General well-being</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Depressed mood</td>
</tr>
<tr>
<td>Sense of positive well-being</td>
</tr>
<tr>
<td>Self control</td>
</tr>
<tr>
<td>General health</td>
</tr>
<tr>
<td>Vitality</td>
</tr>
</tbody>
</table>

FU, follow-up; SD, standard deviation *One patient did not complete the questionnaire at the 6-12 month follow-up
One patient did not complete the PGWB questionnaire at the 6-12 month follow-up. With this exception, there was full compliance to study protocol.

Univariate regression analysis found age, sex, Hunt & Hess grade, shunting for hydrocephalus and PD to be statistically significant predictors for general well-being. In the multivariate analysis, age, sex, Hunt & Hess grade and PD were found to be independent predictors for general well-being.

**Association between PD and general well-being**

*Pituitary dysfunction of any axis.* General well-being scores were consistently lower in patients with evidence of PD when compared to those with normal function. With time, the scores tended to be higher in both groups and differences between the two groups smaller. The effect of PD was statistically significant ($p = .0003$), while the effects of time ($p = .075$) or the interaction between PD and time ($p = .710$) were not. Post-hoc comparisons at each time point showed significantly lower general well-being scores among patients with PD at 3-6 months (85.4 versus 101.7, $p = .017$), and at 6-12 months (90.4 versus 105.3, $p = .021$), but not at 12-24 months (98.9 versus 108.4, $p = .054$) (**Figure 13**). Differences between subscale scores in patients with or without PD were not statistically examined.

![Figure 13](image.png)

**Figure 13.** Mean General well-being scores with 95% confidence intervals for patients with normal pituitary function versus pituitary dysfunction of any axis. There were significant differences at 3-6 months ($p = .017$) and at 6-12 months ($p = .021$), but not at 12-24 months ($p = .054$)

*Central hypoadrenalism.* The same pattern as for PD was seen when comparing those with central hypoadrenalism to those with normal adrenal function with overall lower general well-being and subscale scores in patients with hypoadrenalism. Differences between those with disturbed and normal function became smaller over
time as mean scores for all patients increased. There was a significant effect of hypoadrenalism on general well-being ($p = .0003$) but no significant effect of time ($p = .073$) or interaction between hypoadrenalism and time ($p = .251$). Post-hoc comparisons showed statistically significant differences at 3-6 months (81.6 versus 100.7, $p = .019$), and at 6-12 months (82.2 versus 104.5, $p = .020$), but not at 12-24 months (99.6 versus 105.5, $p = .129$) (Figure 14). There were no statistical analyses comparing subscale scores. However, differences between patients with hypoadrenalism and normal function were particularly marked in the subscales anxiety at 3-6 months (18.5 versus 24.2) and vitality at 6-12 months (11.7 versus 16.8).

![Figure 14. Mean General well-being scores with 95% confidence intervals for patients with normal adrenal function versus hypoadrenalism. There were significant differences at 3-6 months ($p = .019$), and at 6-12 months ($p = .020$), but not at 12-24 months ($p = .129$).](image)

**Growth hormone deficiency.** Comparisons of general well-being scores in patients with GHD and normal somatotropic function are shown in Figure 15. There was no significant effect of either GHD ($p = .937$), time ($p = .612$), or the interaction between GHD and time ($p = .774$) on general well-being scores. At 3-6 months there were only 3 patients with GHD. They had an average general well-being score of 102.7 compared to 97.0 among those those with normal somatotropic function. At subsequent follow-up occasions general well-being scores were 96.2 versus 99.1 at 6-12 months, and 101.2 versus 105.3 at 12-24 months in the groups, respectively. Although subscale scores were not subjected to statistical examination, the differences in subscale scores for vitality at 12-24 months were most pronounced in favor of normal function (15.5 versus 17.6).
Figure 15. Mean General well-being scores with 95% confidence intervals for patients with normal somatotropic function versus growth hormone deficiency (GHD). There was no significant effect of GHD on general well-being.

Resolved, persistent or new onset pituitary dysfunction. The mean change in general well-being for those who had resolved PD between two follow-up occasions was 10.4 (n=8), in those with unchanged PD or normal function 4.2 (n=60), and in those with new onset PD -3.7 (n=15). Differences between groups were statistically significant \( p = .028 \). Post-hoc analysis (Tukey) revealed a significant difference between those with resolved PD and those with new onset PD \( p = .038 \).

Paper IV

Study population

Thirty-six of the initially selected 113 patients were deceased at the time of follow-up. Questionnaires were sent out by mail and eventually 67 persons of 71 returned the requested information, a 94% compliance rate (Figure 16).
Clinical characteristics of the 67 included patients are listed in Table 10. Fifty-four had suffered aneurysmal SAH and 13 SAH of unknown cause. Mean age at ictus was 42.1 years, (range 17-58). Thirty-six (54%) were females. In the aneurysmal SAH cases, the site of the ruptured aneurysm was the anterior communicating artery in 13, the ICA in 20 and the MCA in 21 patients. Mean time from hemorrhage to follow-up was 24.5 years (range 20-28). Average age at follow-up was 66.6 years (range 38-87).

Table 10. Clinical characteristics of the study population in Paper IV

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All respondents (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at SAH (range)</td>
<td>42.1 years (17-58)</td>
</tr>
<tr>
<td>Female sex</td>
<td>36 (54%)</td>
</tr>
<tr>
<td>Aneurysmal SAH</td>
<td>54 (81%)</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>13 (19%)</td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>20 (30%)</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>21 (31%)</td>
</tr>
<tr>
<td>SAH of unknown cause</td>
<td>13 (19%)</td>
</tr>
<tr>
<td>Mean time to follow-up (range)</td>
<td>24.5 years (20-28)</td>
</tr>
<tr>
<td>Mean age at follow-up (range)</td>
<td>66.6 years (38-87)</td>
</tr>
</tbody>
</table>

SAH, subarachnoid hemorrhage
Sleeping disturbances

Insomnia was commonly reported, affecting 17 of 65 respondents (26%). Twelve (18%) experienced problems in initiating sleep and 12 (18%) acknowledged problems maintaining sleep.

Working capacity

After ictus, 61 of 67 individuals (91%) had returned to work. Forty-six of those eventually resumed working to the same extent as before their illness. Fifteen individuals had returned to work at a level below their previous working capacity.

Quality of Life Scale

The QOLS questionnaire was returned by 66 individuals. The mean total score was 90.0. Scores for each of the 16 items are listed in Table 11.

Table 11. Results of the 16 items of the Quality of Life Scale. Means with standard deviations. Each item is scored 1-7, higher scores reflect better outcome.

<table>
<thead>
<tr>
<th>Item</th>
<th>66 respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Material and physical well-being: 6.2 (0.9)</td>
</tr>
<tr>
<td>2</td>
<td>Health: 5.5 (1.5)</td>
</tr>
<tr>
<td>3</td>
<td>Relationships with parents, siblings and other relatives: 5.8 (1.3)</td>
</tr>
<tr>
<td>4</td>
<td>Having and raising children: 6.0 (1.3)</td>
</tr>
<tr>
<td>5</td>
<td>Relationship with spouse or significant other: 6.4 (1.0)</td>
</tr>
<tr>
<td>6</td>
<td>Relationships with friends: 6.2 (0.9)</td>
</tr>
<tr>
<td>7</td>
<td>Helping and encouraging others: 5.7 (1.2)</td>
</tr>
<tr>
<td>8</td>
<td>Participating in organizations and public affairs: 5.0 (1.7)</td>
</tr>
<tr>
<td>9</td>
<td>Intellectual development: 4.7 (1.6)</td>
</tr>
<tr>
<td>10</td>
<td>Understanding of self: 5.7 (1.0)</td>
</tr>
<tr>
<td>11</td>
<td>Occupational role: 5.6 (1.4)</td>
</tr>
<tr>
<td>12</td>
<td>Expressing oneself creatively: 4.7 (1.6)</td>
</tr>
<tr>
<td>13</td>
<td>Socializing: 5.5 (1.3)</td>
</tr>
<tr>
<td>14</td>
<td>Passive and observational recreation: 6.1 (1.0)</td>
</tr>
<tr>
<td>15</td>
<td>Active and participatory recreation: 5.0 (1.8)</td>
</tr>
<tr>
<td>16</td>
<td>Independence, doing for oneself: 6.1 (1.3)</td>
</tr>
</tbody>
</table>

Five items in the scale received a mean rating better than 6 and another 8 items a mean rating between 5 and 6. No item received a score lower than 4. The qualities getting the highest ratings were “relationship with spouse or significant other” (6.4) and “relationships with friends” (6.2). The feeling of “independence, doing for
oneself” was high (6.1) and so were ratings of “material and physical well-being” (6.2) and participation in cultural activities, “passive and observational recreation” (6.1). The lowest ratings were given to “intellectual development” (4.7) and “expressing oneself creatively” (4.7). Linear regression analyses of variables potentially associated with QOLS scores showed that sleeping disturbances and inability to return to work after SAH were significantly associated with lower QOLS scores in both univariate and multivariate models ($p < .01$).

**Psychological General Well-Being**

Average general well-being score was 105.3 in the 66 persons who completed the questionnaire. Dimension scores with normative values are given in Table 12. Average scores in the study population did not differ from reference values. Linear regression analyses of variables associated with PGWB scores showed that sleeping disturbances were significantly associated with lower PGWB scores in both univariate and multivariate models ($p < .01$).

<table>
<thead>
<tr>
<th>Dimension</th>
<th>66 respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>General well-being (total score)</td>
<td>105.3 (101.0-109.6)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>25.0 (23.9-26.1)</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>16.0 (15.5-16.6)</td>
</tr>
<tr>
<td>Sense of positive well-being</td>
<td>16.6 (15.7-17.6)</td>
</tr>
<tr>
<td>Self control</td>
<td>15.6 (15.0-16.1)</td>
</tr>
<tr>
<td>General health</td>
<td>14.4 (13.6-15.2)</td>
</tr>
<tr>
<td>Vitality</td>
<td>17.7 (16.7-18.8)</td>
</tr>
</tbody>
</table>

**Reintegration to Normal Living**

Mean RNL index score was 90.0 for the 67 individuals who completed the questionnaire. Twenty-eight (42%) patients received an index of 100, i.e. they experienced full readjustment to normal living after the illness. Thirty-five (52%) patients scored in the range of 60-99, indicating mild or moderate reintegration difficulties and 4 (6%) scored <60, indicating severe reintegration problems. Content and mean scores for all original RNL items are given in Table 13. The mean index score of the 17 supplementary RNL items was 61.0. Content and mean scores for all items are given in Table 14.
Table 13. Reintegration to Normal Living. Means with standard deviations. Each item is scored 1-10. Higher scores reflect better outcome.

<table>
<thead>
<tr>
<th>Item</th>
<th>67 respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Moving around living quarters</td>
</tr>
<tr>
<td>2</td>
<td>Moving around community</td>
</tr>
<tr>
<td>3</td>
<td>Take trips out of town</td>
</tr>
<tr>
<td>4</td>
<td>Comfortable with self-care needs</td>
</tr>
<tr>
<td>5</td>
<td>Days occupied in work activity</td>
</tr>
<tr>
<td>6</td>
<td>Participate in recreational activities</td>
</tr>
<tr>
<td>7</td>
<td>Participate in social activities</td>
</tr>
<tr>
<td>8</td>
<td>Assume role in family</td>
</tr>
<tr>
<td>9</td>
<td>Comfortable with personal relationships</td>
</tr>
<tr>
<td>10</td>
<td>Comfortable with myself in company of others</td>
</tr>
<tr>
<td>11</td>
<td>Deal with life events as they happen</td>
</tr>
</tbody>
</table>

Table 14. Psychological problem areas following subarachnoid hemorrhage ad modum Reintegration to Normal Living. Means with standard deviations. Each item is scored 1-10. Higher scores imply a better adjustment

<table>
<thead>
<tr>
<th>Item</th>
<th>67 respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Need for daytime rest</td>
</tr>
<tr>
<td>13</td>
<td>Fatigability</td>
</tr>
<tr>
<td>14</td>
<td>Problems with economic management</td>
</tr>
<tr>
<td>15</td>
<td>Staying at home mostly</td>
</tr>
<tr>
<td>16</td>
<td>Lack of interest in others</td>
</tr>
<tr>
<td>17</td>
<td>Poor memory</td>
</tr>
<tr>
<td>18</td>
<td>Difficulty in problem solving/planning ahead</td>
</tr>
<tr>
<td>19</td>
<td>Problems seeing a job through</td>
</tr>
<tr>
<td>20</td>
<td>Lack of concentration</td>
</tr>
<tr>
<td>21</td>
<td>Impulsivity</td>
</tr>
<tr>
<td>22</td>
<td>Making many mistakes</td>
</tr>
<tr>
<td>23</td>
<td>Confused/bewildered</td>
</tr>
<tr>
<td>24</td>
<td>Slow mental processing</td>
</tr>
<tr>
<td>25</td>
<td>Forgetting appointments and similar</td>
</tr>
<tr>
<td>26</td>
<td>Lack of efficiency at work</td>
</tr>
<tr>
<td>27</td>
<td>Less qualified work</td>
</tr>
<tr>
<td>28</td>
<td>Irritability/bad temper</td>
</tr>
</tbody>
</table>

The 11 items of the original RNL scale and the 17 supplementary items were combined and subjected to a factor analysis. This yielded 6 principal factors explaining more than 73% of the total variance. The strongest factor to emerge was related to aspects of Cognition and Mental control (supplementary items 17, 21, 28, 26, 18, 20, 19) followed by Performance Quality (supplementary items 23, 24, 25, 27, 22 and original item 6), Commitment (original items 9, 7, 8, 11 and 10) and Motility (original items 4, 1, 2, 5, 3). The two remaining factors could be labeled Fatigue.
(supplementary items 12 and 13) and *Social Disinterest* (supplementary items 15, 16, 14).
Discussion

Pituitary dysfunction after SAH

In the studied population of 51 aneurysmal SAH patients, endocrine abnormalities were common at all 4 evaluation occasions, from the acute phase after the bleed up to 24 months later. Evidence of PD was seen in 37% in the acute stage, in 27% after 3-6 months, in 34% after 6-12 months, and in 43% after 12-24 months. A recent meta-analysis of PD after aneurysmal SAH, in which the studies of this dissertation were included, the pooled prevalence of any deficiency was 31% after 3-6 months and 25% in studies reporting data later than 6 months after hemorrhage. There were considerable differences between studies, ranging from 8% to 45% in the short-term and from 0 to 55% in the long-term studies.

Central hypoadrenalism

Adrenocorticotropic function was assessed indirectly by measuring morning (9 am) concentrations of cortisol. With the cut-off value of 250 nmol/L between deficiency and normal function, 8% had cortisol levels indicating impaired adrenocortical function in the acute stage, 18% at follow-up after 3-6 months, 20% after 6-12 months and 11% after 12 to 24 months. Other investigators have reported frequencies of secondary adrenal insufficiency between 0 and 21.5% as assessed by basal levels, but cut-off values to define deficiency have varied between studies. During the acute stage, with patients in a critically ill state, higher cut-offs for deficiency could be advocated. Higher cortisol concentrations have been linked with SAH severity in terms of global cerebral edema. However, studies with daily cortisol measurements have shown that concentrations are merely elevated during the first day after SAH, not affecting sampling 5-10 days after ictus.

Based on dynamic testing at the 12 to 24 months follow-up, 30% of those assessed by ITT had central hypoadrenalism, while none of those evaluated by the SST had an abnormal response. The discrepancy between the results of the different dynamic tests is probably explained by their different mechanisms of action. The ITT relies on hypoglycemic provocation of hypothalamic-pituitary function and is considered the method of choice in the diagnosis of central hypoadrenalism.
whereas the SST only tests hypothalamic and pituitary function indirectly. Most previous studies have described the prevalence of hypoadrenalism after SAH as very low based on SST.\textsuperscript{132-134} Our results using ITT are comparable to the findings reported by Kreitschmann-Andermahr et al\textsuperscript{129} who found 40% prevalence of central hypoadrenalism at 12 to 72 months after SAH, but contrasts to the 0% reported by Klose et al\textsuperscript{132} 11 to 26 months after SAH. Both of these studies used ITT and the same cut-off limit for normal function as in this study, i.e. peak cortisol >500 nmol/L.

There was only a partial overlap between the results from basal cortisol sampling and ITT at the last follow-up occasion. All patients that had insufficient cortisol responses to ITT had basal plasma cortisol >250 pmol/L and might easily have been overlooked as normal. On the other hand, 5 patients with plasma cortisol <250 pmol/L, turned out to have normal responses to ITT or SST, which suggests limitations in using basal cortisol concentrations to detect deficiency. None of the patients with unstimulated cortisol concentrations >450 nmol/L had central hypoadrenalism as evaluated by ITT. This is consistent with the view that basal concentrations above this level exclude dysfunction\textsuperscript{114} and may be used as a screening test to exclude post-SAH hypoadrenalism.

**Growth hormone deficiency**

Somatotropic function as assessed by basal IGF-1 concentrations suggested deficiency in 12% in the acute stage, in 20% after 3-6 months, in 20% after 6-12 months and in 29% of patients after 12-24 months. However, IGF-1 used as a biochemical marker for GHD has limitations, concentrations also depend on other factors, such as nutritional status. Thus, a malnourished patient may have low concentrations also without GHD. In other studies, the frequency of GHD based on IGF-1 levels has ranged between 15%\textsuperscript{133,162} and 36.7%\textsuperscript{128} Studies of the dynamics of IGF-1 concentrations during the acute stage after SAH have given conflicting results. One study has shown decreased concentrations,\textsuperscript{163} whereas another has showed increased concentrations\textsuperscript{164} during the first days following SAH.

Dynamic tests were also used to assess somatotropic function. The ITT is the gold standard, but induction of hypoglycemia poses known risks of aggravating ischemic heart disease or eliciting epileptic seizures.\textsuperscript{138} At early follow-up after 3-6 months and for some participants at late follow-up after 12-24 months, ITT was considered too riskful to be employed. For these, the GHRH-arginine stimulation test with cut-off levels adjusted to individual BMI was used instead.\textsuperscript{139} By this test, 7% were diagnosed with GHD after 3-6 months and 14% after 12-24 months. Dynamic evaluation after 12-24 months using the ITT, which is sensitive to both hypothalamic and pituitary dysfunction, showed a frequency of GHD of 30%. The
lowest prevalence reported in other studies has been 0 for both GHRH-arginine stimulation and ITT, and the highest 36.4% and 20%, respectively.

Comparing the different dynamic tests, the ITT detected more cases of GHD than GHRH-arginine stimulation. Likewise, it was only in the group subjected to the ITT that hypoadrenalism could be demonstrated. Due to the inherent selection bias with the exclusion of patients over 65 years of age for the ITT, and the fact that no patients were evaluated by both ITT and SST/GHRH-arginine stimulation, the superiority of one dynamic test over the other cannot be concluded. However, the discrepancy between these tests seems to infer that the ITT is a more sensitive test in patients who are at risk of injury to the hypothalamus. The strength of applying the ITT is that insulin-induced hypoglycemia has more global effects, including hypothalamic stimulation. On the other hand, a pooled analysis has shown the same frequency of GHD based on both GHRH-arginine tests and ITT, 19%.156

Hypogonadism

Gonadotropin deficiency was the most common endocrine abnormality in the acute stage, affecting 30%, but was less common at follow-up; 4% after 3-6 months, 2% after 6-12 months and 11% after 12-24 months. Acute phase dysfunction that later resolves has also been described after TBI and has been argued to be a part of a more general response to severe acute illness.165 It should be pointed out that these results are based on unstimulated values. Thus, an underestimation of the true prevalence of central hypogonadism cannot be excluded. Our results, as well as data from other longitudinal studies, suggest that gonadotropin dysfunction is frequent early after SAH but later restitutes in many patients.131,132,166

Thyrotropic deficiency

Subnormal levels of T4 without appropriate elevation of TSH were interpreted as indicative of thyrotrophic deficiency. This was seen in 6% in the acute stage and 2% after 3-6 months, but not in any patient during later follow-up. This is in accordance with data from other authors. Acute phase decrease of T3 has been described after SAH.164 Both low circulating concentrations of T3 and T4 may represent an unspecific manifestation of critical illness.167 Most other follow-up studies on SAH patients, which have consistently reported low incidences of TSH deficiency,129,131-134,166 with the exception of Aimaretti et al (9.3%).130 Preserved thyrotropic function likely reflects the robustness of this neuroendocrine axis and shows that SAH was not followed by complete hypopituitarism in any case of the present cohort.
Prolactin

Mild elevations of prolactin were seen in 16% in the acute stage, but merely a few cases during follow-up. Other than a direct consequence of SAH, possible causes were the early time of sampling at 9.00 am (local reference values are set for samples obtained after 10.00 am and at least 3 hours after waking up), medication side effects and psychological stress.

Antidiuretic hormone

Based on plasma and urine osmolalities, and excluding the 11 patients requiring treatment for hyponatremia in the acute stage, no single case of SIADH or diabetes insipidus was detected. Water deprivation testing was not conducted, but may have revealed cases of diabetes insipidus not evident from basal values.

Development over time

In most cases, pituitary impairments were either new or had resolved at follow-up compared to the acute stage. Similar findings have also been noted in other longitudinal studies.\(^1\) Acute phase abnormalities that later resolve may be a transient functional response, but may also represent the restorative capacity of the hypothalamic structures involved. On the other hand, endocrine abnormalities that become apparent in later phases, may initially have been masked by an acute neuroendocrine response to severe disease or may represent delayed secondary injury mechanisms. Whereas no differences in study design seem to explain the divergent findings on the incidence of pituitary dysfunction in this and other studies, this variability over time may contribute to the conflicting data reported. Our data carries the limitation that assessment of central hypoadrenalism and GHD was assessed indirectly at most occasions. The best assessment for the development of PD over time would be to perform the ITT repeatedly during follow-up.

Relation to SAH characteristics

The relationship between endocrine abnormalities and clinical SAH characteristics was examined. Patients with pituitary dysfunction in the acute stage were significantly more likely to have SAH from an aneurysm in the circle of Willis (ACoA, ICA or basilar apex) than other locations (MCA or pericallosal artery). This could be due to the close anatomical relationship between the circle of Willis and the hypothalamus and pituitary stalk. Furthermore, patients with hypopituitarism were more likely to
have had their aneurysms treated by endovascular technique. This is at least in part due to a propensity to coil basilar apex and to clip MCA aneurysms and thus biased by location. At follow-up after 3-6 months patients with pituitary dysfunction were significantly younger than those with normal function. This was also found to be the case in the 12 month post-SAH evaluation by Gardner et al.\textsuperscript{\textregistered} This relationship was not found at any other follow-up occasion in our study.

Six of 48 patients had lesions in the hypothalamus visible on MRI. All of these had evidence of PD at some point during the study. However, in the majority of patients with PD, hypothalamic MRI lesions were not detected. Injury from hemorrhage and ischemia in the hypothalamus has been shown to be common after aneurysmal SAH, a study on autopsy findings reported this in 61\% of patients.\textsuperscript{127} Many of these lesions are probably too small to be detected with MRI presently available for clinical use. Given the high prevalence of organic hypothalamic defects revealed by histopathological diagnosis, the development of PD after SAH is not surprising.

### Pituitary dysfunction and outcome after SAH

Functional outcome was graded according to GOS. This grading scale is commonly used to assess outcome after SAH, but can be seen as too blunt to detect subtle impairments in cognitive function and physical ability that usually are attributed to endocrine dysfunction. We presented comparisons of medians and found that PD in the acute stage was associated with a lower median GOS score at discharge. During follow-up, PD after 3-6 months was also associated with lower median GOS scores, but not at later occasions.

### Implications for QoL

In want of a QoL measure specifically designed for SAH patients, the PGWB index was chosen as the most suitable. Evaluation by this instrument showed a positive trend over time, from a mean general well-being score of 97.3 at 3-6 months to 104.3 at 12-24 months, surpassing the mean score of the reference population.\textsuperscript{143} However, this improvement was not statistically significant. Multivariate regression analysis determined age, sex, Hunt & Hess grade and PD as independent predictors for PGWB score. The association to age and sex resembled what was described in the reference population, with higher scores with increasing age and in male study subjects.\textsuperscript{143} Poor clinical grade at admission has previously been identified as a risk factor for follow-up QoL impairments.\textsuperscript{100} Patients with evidence of PD in our cohort had significantly lower general well-being scores. Analysis of individual endocrine axes
showed that this was explained by lower scores in patients with HPA-axis dysfunction. Growth hormone dysfunction was, however, not associated with lower general well-being scores.

At early follow-up after 3-6 months, mean general well-being scores in patients with PD were very low (85.4) compared to those with normal pituitary function (101.7). Comparing with other studies using the PGWB index, this score was also lower than in patients with severe gastroesophageal reflux disease (89)\textsuperscript{145} and male patients awaiting bypass surgery for angina pectoris (92.1)\textsuperscript{168} and comparable to patients undergoing treatment for stress-related exhaustion (86.0).\textsuperscript{169} With time, differences in mean general well-being scores between patients with PD and normal function tended to become smaller, suggesting that PD has a greater impact on early outcome. This would be in accordance with the finding that patients with PD had impaired functional outcome according to GOS during early but not late follow-up. Strengthening the relationship between PD and QoL, resolution of the endocrinopathy was associated with improved general well-being scores, whereas new onset dysfunction was associated with worsening scores.

Central hypoadrenalism was the individual endocrine axis of greatest importance for QoL. This is in accordance with findings by Kreitschmann-Andermahr et al, who have reported associations between hypothalamic-pituitary-adrenal axis dysfunction 27 months after SAH and several psychological aspects of QoL.\textsuperscript{90} In their study, regression analysis identified basal cortisol concentrations as the most important predictor of QoL impairments. In our longitudinal study, the relative differences were particularly marked in the subscales anxiety at 3-6 months and vitality at 6-12 months. Anxiety seems to be a common constituent of reduced QoL after SAH. As assessed by the Hospital Anxiety and Depression Scale, it has been reported in 11-59% of SAH patients.\textsuperscript{86,89,91} Vitality is the subscale that corresponds best to fatigue, which is main symptom of chronic adrenal insufficiency.\textsuperscript{137}

Reduced QoL in adult GHD from causes other than SAH has been demonstrated before.\textsuperscript{124,170} Surprisingly, QoL impairment with GHD was not observed in the present study. However, absolute numbers of GH deficient patients at the 3-6 and 6-12 month follow-up occasions were relatively small, making interpretation less certain. On the other hand, our findings are in keeping with data from Kreitschmann-Andermahr et al, who have reported a correlation between GHD and NHP subscale energy, but not between GHD and any other QoL parameter evaluated.\textsuperscript{80} There is a strong correlation between the NHP energy and PGWB vitality subscales.\textsuperscript{171} Comparing patients with and without GHD in our material, mean scores for vitality after 12-24 months showed the greatest difference in favor of normal GH function. In a study on post-traumatic hypopituitarism, where GHD was the most commonly affected axis, NHP energy was also significantly reduced.\textsuperscript{172} A specific measure for QoL in adult GHD, the QoL-AGHDA,\textsuperscript{173} has failed to show an association between impaired QoL and GHD after SAH.\textsuperscript{90}
In defining endocrine deficiencies of hypothalamic and pituitary origin, different methods were used at different follow-up occasions. This was in part for reasons of patient safety. The ITT, which is the gold standard for diagnosing central hypoadrenalism and GHD, involves hypoglycemia, which was considered to carry too much risk early after SAH. Comparing PGWB scores in patients with deficient and normal pituitary function was, therefore, based partly on results from basal hormone concentrations and partly on dynamic tests. For the statistical interpretation, this might be argued against. However, we deemed it appropriate to use the best available assessment at any given time. At the last follow-up occasion, when PGWB score differences between pituitary deficient and non-deficient patients were least pronounced, assessment of both hypoadrenalism and GHD were made by dynamic tests. The question rises whether the dynamic tests may be too sensitive, revealing latent, clinically insignificant abnormalities.

Reduced health-related QoL after aneurysmal SAH is clearly influenced by many factors. Although this study strongly supports that PD affects QoL, we would not argue for PD as the sole cause of the problem. Cognitive defects, subtle or pronounced, post-traumatic stress and the strain of psychosocial consequences, such as being unable to return to former work or broken up personal relationships are also likely to be of importance. However, disturbed endocrine function that results from hypothalamic and pituitary injury is important to recognize, not least as its symptoms may be amenable to hormone replacement. It is noteworthy that in the patient population studied, health related QoL was not reduced in the group as a whole, whereas individuals, particularly those with evidence of hypoadrenalism, had a pronounced QoL impairment.

**Other implications for outcome after SAH**

Impaired pituitary function after SAH may have other clinical implications. Increased risk of vascular mortality after aneurysmal SAH has been reported; premature vascular death is also seen in patients with pituitary dysfunction, probably secondary to changes in lipid regulation caused by GHD. Somatotropic function was indeed the most commonly affected endocrine axis in this and other studies on SAH patients. Patients with history of SAH may be subjected to late surgical interventions, such as aneurysm-occluding and CSF-shunting procedures. The integrity of the HPA axis may affect the clinical course during and after surgical interventions and should be considered in the pre-operative work-up in patients who have suffered from SAH.
Long-term follow-up after SAH

The long-term study population included both patients with aneurysmal SAH and SAH of unknown cause, all with a good neurological recovery after 1 year, as assessed by standard outcome measures. They were all referred for neuropsychological assessment between 3 and 7 years after ictus. At this point in time, functional morbidity was demonstrated in terms of intellectual impairment and problems of readjustment.65,144-146

Given such cognitive disturbances in these good grade SAH patients, one might expect persistent shortcomings in daily life with consequences for self-realization, emotional, social and marital adjustment, work, leisure activities and similar in the years subsequent to the bleed. Indeed, this was reflected in the reintegration difficulties reported through the supplementary questionnaire ad modum RNL in the present evaluation. Evidently, these phenomena do not seem to wane over time, but their impact may be felt for a great many years after the bleed.

Quality of life, as assessed by QOLS and PGWB, was not reduced in the study population as a whole. Although studies on long-term QoL follow-up after SAH are scarce, similar findings have been reported. Assessment by Short Form-36 in patients with good recovery (GOS 5) 4.7 years after SAH did not show significant reductions compared to health controls except with respect to general health and social functioning.99 Evaluation by EQ-5D 10 years after SAH revealed reduced indexes compared to controls. In patients with favorable outcome (GOS 4-5) this reduction was only modest.98 In our cohort studied with concomitant endocrine evaluation, PGWB scores followed a positive trend, surpassing reference scores after 12-24 months. In our long-term follow-up material, the average total QOLS score of 90.0 equals the approximately 90 stated for healthy controls,147 and the mean total PGWB score of 105.3 compares favorably to the norm value of 102.9.145 However, relative QoL impairments were seen in subgroups. Of the two QoL measures, QOLS is more oriented towards social aspects, whereas PGWB is more oriented towards health-related issues. This is likely reflected in lower QOLS scores but not lower PGWB scores among those unable to return to work. With respect to gender, PGWB scores tended to be lower for females, but this difference was not statistically significant. This trend was also in agreement with normative data. Sleeping disorders were associated with impaired QoL as measured with both QOLS and PGWB. Comparing with data from other investigators, sleeping disturbances in our cohort (26%) were roughly as common as what has been reported 1-3.4 years after SAH (34%)95 and 4-7 years after SAH (26%).78 They were also similarly associated with reduced QoL.95

In the assessment of long-term adjustment and reintegration, no single inventory was found to comprise all subject areas of presumed importance. In view of such limitations of existing inventories, relevant subject areas were then compiled into a supplementary RNL scale to elucidate aspects known to be sensitive to the effects of
SAH. The factor analysis performed on the original and supplemental RNL items revealed diverse aspects of reintegration and adjustment. Whereas the original scale primarily addressed aspects of commitment and social participation, the supplementary scale contributed information related to cognition and mental control as well as energy management and executive functioning, aspects not covered by the original RNL scale. Clearly, the factors emerging from the factor analysis represented different but nevertheless significant expressions and dimensions of underlying difficulties during years of readjustment and adaptation. Except for item 6, the original RNL scale was left uncompromised and pure. The additional items provided specific information sensitive to circumstances possibly emerging from the SAH as evidenced in the original studies on these patients in the intermediate years following the bleed. Among these supplementary items specifically devised to address psychological and neuropsychological problems commonly seen after SAH, i.e. fatigue, disturbance of mood and affect, lack of commitment and aspects of cognitive impairment, the findings were consistent in quality with what was observed in the original evaluation. None of the items of the original RNL scale stood out as particularly severely affected and no single mean score in the supplementary scale exceeded the lowest mean score in the original RNL scale. The mean index score of the 17 supplementary items was considerably lower than the index for the original items, 61.0 versus 90.0.

Other authors have presented data on RNL after SAH. Fourteen months after SAH from ACoA aneurysms, mean RNL was 84; 14% reported no reintegration difficulties, 78% had mild to moderate difficulties and 8% severe difficulties. Patients who had been in good neurological condition on hospital admission, showed impaired reintegration in 45% 1-5 years later. Our data confirms that such problems may persist for over 20 years after SAH.

The major limitation of this study pertains to the characteristics of the SAH patients in the original studies. Only SAH survivors with good 1-year recovery were selected and eventually became the participants of the present study. Thus, the results are probably not applicable to poor grade patients. Another limitation inherent to the study design lies in the passing of many years before follow-up. This will make younger patients (at the time of SAH) more likely to be included. However, the clinical course for this subgroup of SAH patients is particularly important to examine. Identifying factors associated with increased risk of reduced QoL may help improve the care of these patients over very long time.
Conclusions

- The studies demonstrate high frequencies of PD from the acute phase until 2 years after aneurysmal SAH. The results stress the value of dynamic testing, which includes evaluation of the integrity of hypothalamic neuroendocrine function. Unless contraindicated, the ITT should be used to evaluate the adrenocorticotropic and somatotropic axes. Acute PD was more common in patients with ruptured aneurysms in the circle of Willis compared to other sites, giving support to the hypothesis of direct injury from the bleed to hypothalamic structures as the pathogenic mechanism. Furthermore, PD was associated with less favorable functional outcome, both in the acute stage and at follow-up after 3-6 months. (Paper I & II)

- We found a significant effect of PD on health-related QoL in patients recovering from aneurysmal SAH. This was on account of disturbances in HPA-axis function. The findings suggest an important role for hypoadrenalism for QoL impairments following SAH. Future studies should investigate the possibilities for hormone replacement therapy in this group of SAH survivors. (Paper III)

- Averaging 24.5 years after spontaneous SAH, we found no reduction in QoL as measured by the QOLS and PGWB indexes. However, impaired QoL was seen in subgroups: in those with sleeping disorders and in those who had not been able to return to work after SAH. A significant share still experienced reintegration difficulties although QoL was good and equaled that of a healthy population. The results shed new light on the course of recovery following SAH, and emphasize the need for rehabilitation efforts and continuous support over long time also in patients with apparently good functional outcome. (Paper IV)
Spontan subaraknoidalblödning (SAB) är en mycket allvarligt sjukdom. Tillståndet har inte sällan dödlig utgång och de som överlever drabbas ofta av neurologiska skador som kan innebära bestående handikapp. Sådana följdverkningar kan ibland vara subtila men ändå ytterligt plågsamma för den drabbade och karaktäriseras många gånger av koncentrationssvagheter, initiativlöshet, trötthet och sömnstördningar. Detta är förknippat med försämrad livskvalitet. Man vet att dessa symptom kan hålla i sig i flera år, men det finns inga studier som visar hur det går på längre sikt än ungefär ett decennium. På senare tid har man uppmärksammat likheter mellan följdtillståndet efter SAB och de symptom som uppträder vid skador i hypothalamus och hypofysen, som är de delar av hjärnan som styr all hormonell aktivitet i kroppen. Anatomiskt är dessa strukturer belägna så att de löper stor risk att skadas vid SAB, och oavsett skadorns lokalisation ger de sviktande hypofysfunktion.

De vetenskapliga arbetena som utgör denna doktorsavhandling utformades dels med syfte att studera förekomst av hormonella störningar under de första två åren efter SAB, dels med syfte att undersöka samband mellan sådana skador och störd livskvalitet, och slutligen med syfte att studera återhämtning och livskvalitet under ett mycket längre tidsperspektiv, över 20 år, efter SAB.

I delarbete I och II presenteras resultaten av den hormonella utvärderingen. Vi fann att en stor andel av de studerade patienterna uppvisade tecken på hypofyssvikt. Av de hormonella system eller axlar som styrs av hypofysen var tillväxthormonbrist och störd binjurebarksfunktion vanligast.

I delarbete III presenteras uppföljning av psykologiskt välbefinnande under samma tidsperiod som den hormonella utvärderingen. Här fann vi en tydlig koppling mellan försämrad livskvalitet och sviktande hypofysfunktion, framförallt vid nedsatt insöndring av binjurebarkhormon.

I delarbete IV presenteras långtidsresultaten, där vi fann att återhämtningssvagheter föreligger även i ett tidsperspektiv på över 20 år efter SAB. I gruppen som helhet märks inte nedsatt psykologiskt välbefinnande, däremot hos undergrupper, nämligen de som inte kunnat återgå till arbete efter blödningen och de med sömnsvårigheter.

Sammanfattningsvis talar studierna för att hypofyssvikt är vanligt förekommande efter SAB, samt att det finns ett samband mellan sänkt livskvalitet och sådan sviktande funktion. Detta talar för att det är viktigt att identifiera hormonella störningar i efterförloppet av SAB. Vidare visas att merparten av de som drabbats av
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