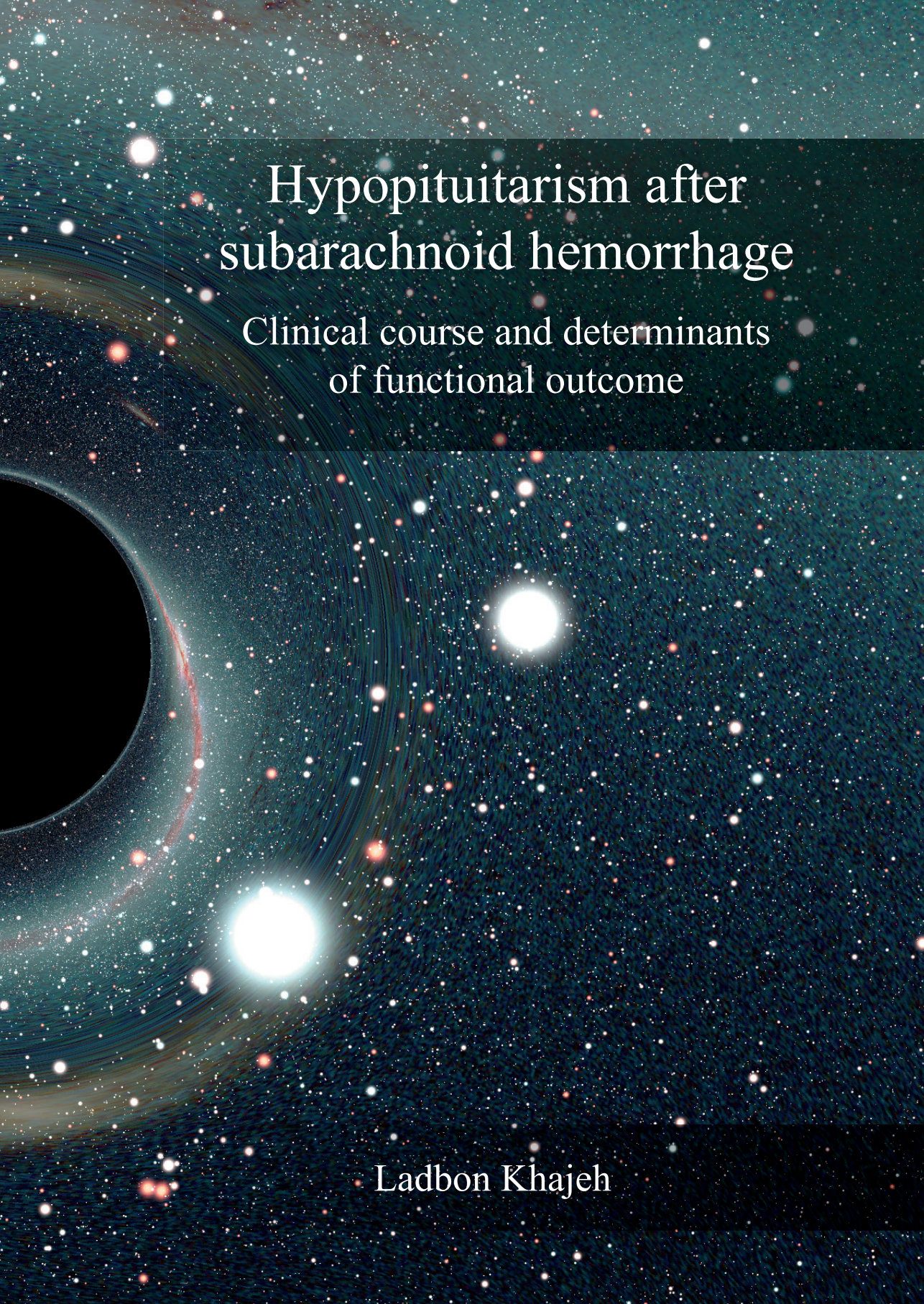

Hypopituitarism after subarachnoid hemorrhage

Clinical course and determinants of functional outcome

Ladbon Khajeh

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Hypopituitarism After Subarachnoid Hemorrhage,

Clinical course and determinants of functional outcome

Hypopituitarisme na een subarachnoidale bloeding,
Beloop en klinische determinanten van lange termijn uitkomst

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus
Prof. dr. R.C.M.E. Engels
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

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geboren te Teheran, Iran

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	Prof. dr. A.J. van der Lelij, secretaris
	Prof. dr. J.J. van Busschbach

Contents

Chapter I

General Introduction

Subarachnoid Hemorrhage

Subarachnoid hemorrhage is a severe and life-threatening disorder. Subarachnoid hemorrhage is defined as hemorrhage into the subarachnoid space. It is often due to rupturing of an aneurysm or an arteriovenous malformation[1].

In the Netherlands, aneurysmal subarachnoid hemorrhage (SAH) has an incidence rate of 5.7 per 100.000 person years for men and 9.9 per 100.000 person years for women[2]. SAH is associated with high, but declining mortality rates. This has been attributed to new micro-neurosurgical and endovascular techniques, as well as improvements in intensive care[1, 3, 4]. In 2016 a total number of 1.599 patients were admitted to the hospital in the Netherlands due to SAH with a mortality of 337 (21%) cases[5].

Recovery to an independent life with at most only minor neurological deficits is considered a good neurological outcome[4]. Glasgow Coma Scale (GCS), Hunt&Hess Scale, age, cardiac history, smoking, hypertension, new-onset seizures and mean S100B-protein levels are as far as we know the best predictors for functional outcome after SAH[6-10]. Despite increasing percentages of patients with so-called good neurological outcome, patients within this group often report headache, fatigue, lack of initiative, reduced independence in daily activities, mood disturbances, disturbance of memory/attention capacity, and weight gain. The cause of these symptoms in SAH survivors with an otherwise good neurological outcome remains unexplained[3, 4].

Hypopituitarism and SAH

The symptoms in long term SAH survivors show similarities with symptoms of patients diagnosed with hypopituitarism[3, 4, 30]. As the symptoms of SAH survivors resemble symptoms of hypopituitarism, it is tempting to suspect a relation between SAH and hypopituitarism. Adequate therapy of pituitary deficiencies than could lead to improvement of outcome of SAH survivors. The presence of hypopituitarism in SAH patients has been studied and it has been suggested that SAH may lead to (partial) hypopituitarism and corresponding neuroendocrine dysfunction[3, 4, 24, 27, 31, 32]. However, prevalence rates of hypopituitarism after SAH vary widely between 0 and 55% in recent clinical studies[3]. The growth hormone axis seems to be the most frequently affected, followed by the gonadotropin axis[3, 27, 31]. Potential causes of hypopituitarism after SAH are toxic and inflammatory changes of the hemorrhage, ischemia by vasoconstriction, increased cranial pressure, hydrocephalus or local tissue destruction during neurosurgery[4, 24, 30, 31]. Hemorrhage, necrosis and fibrosis of the anterior pituitary and hypothalamus after SAH have been recorded in post mortem studies[30, 33] supporting the notion of damage to the pituitary after SAH.

Long-term symptoms of patients with previous SAH

In patients who have survived SAH, high rates of functional limitations have been reported, along with quality-of-life impairment, such as fatigue, decreased mobility, loss of motivation, reduced independence in activities of daily living and decreased social functioning.[11] In up to 75% of patients impairments in different cognitive domains such as memory, executive functioning and language, have been reported, depending on the domain measured[12]. Up to 70% of SAH survivors is unable to return to previous work even up to 4 years after SAH[13]. This eminently shows that they suffer from restrictions in performing normal daily activities, even years after SAH.

Fatigue is one of the common long-term potential symptoms of SAH[14]. It is a disabling symptom that has a negative effect on health-related quality of life[15]. Fatigue is often described in general population but pathological fatigue is also present as a symptom in different specific patient populations with various neurological disorders[16, 17]. Physiological fatigue is described as a state of general tiredness which is caused by overextension and ameliorated by rest[18]. It is different from pathological fatigue which is excessive and does not respond to rest[19]. The persistence of pathological fatigue in SAH patients is still not understood. Various mechanisms were theorized among which systemic inflammation after SAH. In this theory proinflammatory cytokines effect the brain leading to altered neurotransmitter signaling by changing enzyme activity, such as indoleamine 2,3-dioxygenase, which in theory can lead to fatigue[20]. Another theory is disruption of frontal-subcortical neuronal circuits due to complications of SAH, such as delayed cerebral ischemia or hydrocephalus[17]. Furthermore damage of the ascending reticular activating system in the brainstem and other parts of the brain can lead to post stroke fatigue[21]. These theories have many uncertainties and up to now there is no evidence for either one of these theories[20]. Impairment of physical fitness is another potential cause of poor functional outcome as it can restrict the level of participation in daily activities[22]. Although it seems similar to fatigue, impaired physical fitness is different from subjective fatigue which is difficult to measure. Impairment in physical fitness can be observed or measured by testing patient performance by repetitive physical or mental tasks[23].

As a novel mechanism, neuroendocrine dysfunction has been postulated as endocrine dysfunction by hypothalamic–pituitary disease, which can lead to changes in body weight, sleep disturbance. and also to fatigue, all symptoms which are frequently present in SAH survivors[21].

The long hypophysis portal vessels and the position of the pituitary stalk make the pituitary sensitive to hypotension, hypoxia or raised intracranial pressure[26]. SAH patients may experience such forces which was stablished mostly in cross sectional studies and case reports[24, 27]. Adrenocorticotropic and thyroid stimulating hormone (TSH) deficiency may cause fatigue, weakness, headache, altered mental activity, and impaired memory. Growth hormone deficiency (GHD) may cause lack of vigor, fatigue, decreased exercise tolerance and decreased social functioning. Gonadotropin deficiency

in women leads to oligomenorrhea, dyspareunia, infertility and loss of libido. In men it can present with impaired sexual functioning, mood impairment, and loss of libido. Antidiuretic hormone deficiency leads to polyuria and polydipsia[28].

The methodology for diagnosing hypopituitarism depends on the axis of the pituitary that is being measured. Furthermore, there are different ways to measure hypopituitarism. For some hormones such as growth hormone and adrenocorticotropic hormone (ACTH), low basal concentrations alone are not sufficient to base a diagnosis on, due to the pulsatile, circadian or situational secretion of the hormones. ACTH and cortisol secretion follow a diurnal rhythm with highest levels in the morning and lowest levels around midnight[29]. For diagnostic accuracy there is a need for stimulation tests to assess malfunction of the ACTH axis. For this reason different dynamic tests have been developed and were used, among which the insulin intolerance test and the metopiron test[28].

GHD also needs to be diagnosed by a stimulation test with different dynamic tests available. The insulin intolerance test is often used and so is the growth hormone releasing hormone (GHRH)-arginine test. Both tests are well tolerated and practical in use. The diagnosis of GHD requires the use of a dynamic, stimulatory test, as basal hormone levels of growth hormone (GH) or insulin-like growth factor (IGF-I) cannot discriminate entirely between insufficient GH secretion and normal GH secretion. Presently, it is not known whether a GH provocative test shortly after SAH can be used safely and if it can identify subjects with persistent GHD. Ghrelin is a potent GH secretion stimulator that can be used for the diagnosis of growth hormone deficiency, without side effects limiting its use. Therefore, a Ghrelin test could represent a suitable test in the setting of testing subjects for GHD shortly after SAH.

The aim of this thesis

The aim of this study is to provide an answer to the following research questions:

1. What is the incidence of hypopituitarism after SAH, and what are its determinants?
2. What is a reliable screening method for detecting hypopituitarism after SAH?
3. What is the relation between SAH, hypopituitarism after SAH and fatigue?
4. How does hypopituitarism affect long-term functional outcome after SAH in comparison to common population?

We will review literature on the existing knowledge of hypopituitarism after SAH. We strive to establish hypopituitarism early after SAH by using a battery of laboratory tests which can be used safely soon after SAH. The incidence of hypopituitarism in patients after SAH will be determined by using this routine hormonal screening protocol. Identification of objective prognostic neurological determinants for the development of hypopituitarism following SAH is another goal of this thesis. At last we aim to evaluate

the effect of SAH and hypopituitarism on fatigue by using a standardized questionnaire and objective physical fitness measurements.

This thesis was performed as a part of a large project which focuses on long-term consequences after SAH. The HIPS study as a part of this project was a prospective single-center observational cohort study. It was registered and approved by the IRB at Erasmus MC University Medical Center, and registered in the Dutch trial registry (NTR 2085). The department of Neurology, Endocrinology and Rehabilitation Medicine of the Erasmus MC, Rotterdam coordinated this study. The aim of this project was to establish the most optimal set of measurement instruments for the evaluation of the consequences of SAH, hypopituitarism and to identify determinants of functional outcome. An earlier thesis by this study group focused on evaluating the long-term consequences 4 years after subarachnoid hemorrhage, and defining which patients are in need of long-term professional support, published in the thesis 'Subarachnoid Hemorrhage: a study on long-term consequences' by W. Boerboom.[34-36] A second thesis 'Subarachnoid Hemorrhage Physical fitness, physical activity and sedentary behavior in the first year after subarachnoid hemorrhage' by W. Harmsen focused gaining insights in the level of physical fitness, physical activity and sedentary behavior in the first year after a-SAH. [37-40]

Outline of this thesis

Chapter 2 is a systematic review of the literature concerning occurrence and clinical manifestation of hypopituitarism after SAH and risk factors for hypopituitarism after SAH. **Chapter 3** evaluates the validity and safety of the Ghrelin test as an early screening instrument for growth hormone deficiency after SAH. The diagnostic value of the ghrelin test was compared with the GHRH arginine test in the diagnosis of growth hormone deficiency. **Chapter 4** outlines the frequency and course of hypopituitarism in a prospective follow up study, assessing hypopituitarism by using a standardized laboratory test, and the search for possible clinical determinants for hypopituitarism after SAH. **Chapter 5** focuses on the relation between hypopituitarism and fatigue as an important complaint of SAH survivors. We prospectively measured fatigue over time by using Fatigue Severity Scale and studied the association of fatigue with hypopituitarism and other established clinical determinants. **Chapter 6** evaluates the physical fitness of SAH survivor's over time by measuring cardiorespiratory fitness and knee muscle strength in relation to hypopituitarism and other clinical determinants on physical fitness. In **Chapter 7** the main findings are presented and discussed in light of the clinical implications and the recent literature. Finally, the raised questions and directions for future research are discussed.

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2

Chapter 2

Hypopituitarism after subarachnoid haemorrhage, do we know enough?

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Abstract

Background: fatigue, slowness, apathy and decrease in level of activity are common long-term complaints after a subarachnoid haemorrhage (SAH). They resemble the symptoms frequently found in patients with endocrine dysfunction. Pituitary dysfunction may be the result of SAH or its complications. We therefore hypothesized that it may explain some of the long-term complaints after SAH. We reviewed the literature to clarify the occurrence, pattern and severity of endocrine abnormalities and we attempted to identify risk factors for hypopituitarism after SAH. We also assessed the effect of hypopituitarism on long-term functional recovery after SAH.

Methods: in a MEDLINE search for studies published between 1995 and 2014, we used the term subarachnoid haemorrhage in combination with pituitary, hypopituitarism, growth hormone, gonadotropin, testosterone, cortisol function, thyroid function and diabetes insipidus. We selected all case-series and cohort studies reporting endocrine function at least 3 months after SAH and studied their reported prevalence, pathogenesis, risk factors, clinical course and outcome.

Results: we identified 16 studies describing pituitary function in the long term after SAH. The reported prevalence of endocrine dysfunction varied from 0 to 55% and the affected pituitary axes differed between studies. Due to methodological issues no inferences on risk factors, course and outcome could be made.

Conclusions: neuroendocrine dysfunction may be an important and modifiable determinant of poor functional outcome after SAH. There is an urgent need for well-designed prospective studies to more precisely assess its incidence, clinical course and effect on mood, behaviour and quality of life.

Introduction

Subarachnoid haemorrhage (SAH) accounts for 5% of stroke deaths and for more than a quarter of potential life years lost by stroke. The incidence of SAH in Western Europe is 10.5 per 100.000 persons per year and varies between regions. Case fatality ranges between 32 and 67% and about a third of patients remain dependent [1,2]. The cause of SAH is a ruptured aneurysm in 85%, perimesencephalic haemorrhage in 10%, and rare conditions in 5% of the cases [3]. Even after a good neurological recovery, a considerable proportion of patients have symptoms interfering with daily life. Fatigue, cognitive and affective dysfunction [4-7], decrease in level of activity and social participation and hence, quality of life, have been described in these patients [5]. Physical disability, social-economic status, personality, stressful events preceding SAH and life threatening illness may each contribute to the performance state of patients after SAH [4,8-11]. Glasgow Coma Scale (GCS), Hunt & Hess Scale, age, cardiac history, smoking, hypertension, new-onset seizures and mean S100B-protein levels are some of the predictors for functional outcome after SAH [12-16].

In recent years, associations have been made between SAH and hypopituitarism [17,18]. In 1914, Simmonds first described hypopituitarism as the inability of the pituitary gland to produce sufficient hormones to meet the needs of the organism. It can be caused by dysfunction of the gland itself or by an insufficient supply of hypothalamic-release-hormones. In general, hypopituitarism is a chronic condition and remains present for life [19]. Adrenocorticotropic (ACTH) and thyroid stimulating hormone (TSH) deficiency may cause fatigue, weakness, headache, altered mental activity, and impaired memory [19,20]. Growth-hormone deficiency (GHD) may cause lack of vigour, fatigue, decreased exercise tolerance and decreased social functioning [19,20]. Luteinizing hormone (LH) and follicle- stimulating hormone (FSH) deficiency in women lead to oligomenorrhea, dyspareunia, infertility and loss of libido. Testosterone deficiency in men can present with impaired sexual functioning, mood impairment, and loss of libido [19,20]. Antidiuretic hormone deficiency (ADH) leads to polyuria and polydipsia [19-21]. Many of the long-term symptoms after SAH show similarity to those occurring in patients with untreated hypopituitarism. Therefore, neuroendocrine dysfunction may be the cause or a contributing factor for residual symptoms after SAH. If this is true, deficient hormones can be supplied which may lead to improvement of these residual symptoms and improvement of long-term outcome after SAH. Nevertheless, hypopituitarism are easily overlooked after SAH and a need for routine assessment of the pituitary axes after SAH has been suggested [17].

The current review concerning neuroendocrine dysfunction in patients surviving SAH is aimed at assessing its incidence, clinical manifestation and risk factors. Furthermore, the effects of neuroendocrine dysfunction on clinical symptoms and functional outcome in patients with SAH are studied.

Methods

Search strategy

We searched Pubmed and Embase for articles published from 1995 to 2014 and used a combination of the term "subarachnoid haemorrhage" with "pituitary function", "hypopituitarism", "growth hormone", "thyroid function", "growth hormone", "cortisol", "gonadotropin", "testosterone function" and "diabetes insipidus". We also searched the reference lists of the articles identified by our search strategy. Two authors (LK, FK) screened titles and abstracts of all references listed in the search results independently. Of the remaining titles, full-text articles were retrieved and again screened for eligibility by both authors independently. In case of disagreement, consensus was sought through discussion. A third author (DD) was available if consensus could not be reached.

Selection criteria

A full-text article was included in this review if it met all of the following criteria: 1) the study population consisted of patients with SAH caused by a ruptured aneurysm or, of a subgroup of patients with aneurysmal SAH; 2) the primary aim of the study was to investigate the incidence of endocrine dysfunction after SAH; 3) outcome was described in terms of levels of one or a combination of the following: ACTH, GH, TSH, cortisol, FSH, LH or testosterone, with a clear description of the assays; 4) time to laboratory investigation was at least 3 months after SAH; and 5) the study concerned a series of patients.

Quality assessment

The two reviewers independently judged all studies by inception cohort, description of source population, description of inclusion criteria, follow-up more than 3 months, description loss to follow-up, standardized or valid measurements and data presentation of most important outcome measures. Items were scored as positive, negative or inconclusive (Table 1). A completed PRISMA checklist for quality assessment has been added as an Additional file 1. Data presented in de studies were then collected. Information on patient and study characteristics, inclusion and exclusion criteria, laboratory and outcome measurements were gathered from the selected articles.

Table 1. Summary of study characteristics of studies included in this literature review

	Study design	Inclusion criteria	Exclusion criteria	Selection bias	Lost to FU nr	Dynamic tests	Analysis	Results
Aimaretti et al. [37]	Prospective cohort	-	-	yes	0	GHRH-arg	+	+
Brandt et al. [33]	Case series	+	+	yes	0	TRH test & ITT (7 out of 10 pts)	+	+
Dimopoulou et al. [17]	Retrospective cohort	+	+	yes	0	none	+	+
Kreitschmann-Andermahr et al. [35]	Retrospective cohort	+	+	yes	10	TRH-LHRH test & ITT	+	+
Aimaretti et al. [32]	Prospective cohort	-	-	yes	0	GHRH-arg	+	+
Kreitschmann- Andermahr et al. [36]	Case series	+	+	yes	8	ITT (14 out of 45 pts)	+	+
Jovanovic et al. [34]	Case series	+	+	yes	0	none	+	+
Tanriverdi et al. [39]	Prosective cohort	+	+	no	0	GHRH-arg & glucagon test	+	+
Klose et al. [40]	Prospective cohort	+	+	no	0	ITT (GHRH-arg if contraindicated)	+	+
Lammert et al. [38]	Prospective cohort	+	+	yes	4	ACTH stimulation test (ITT in some patients)	+	+
Dutta et al. [46]	Retrospective cohort	+	+	yes	0	none	+	+
Gardner et al. [41]	Prospective cohort	+	+	no	0	GHRH-arg and glucagon test	+	+
Khursheed et al. [43]	Prospective cohort	+	+	no	0	none	+	+
Kronvall et al. [44]	Prospective cohort	+	+	no	6	GHRH-arg	no	no
Karaca et al. [45]	Prospective cohort	+	+	no	2	Glucagon test	+	+
Blijdorp et al. [42]	Prospective cohort	+	+	yes	0	Ghrelin test and GHRH-arg, Synacten test in some patients	+	+

+: inclusion criteria, exclusion criteria, assessment methods and results clearly defined and reflected, -: inclusion criteria, exclusion criteria, assessment methods and results not or not clearly defined.

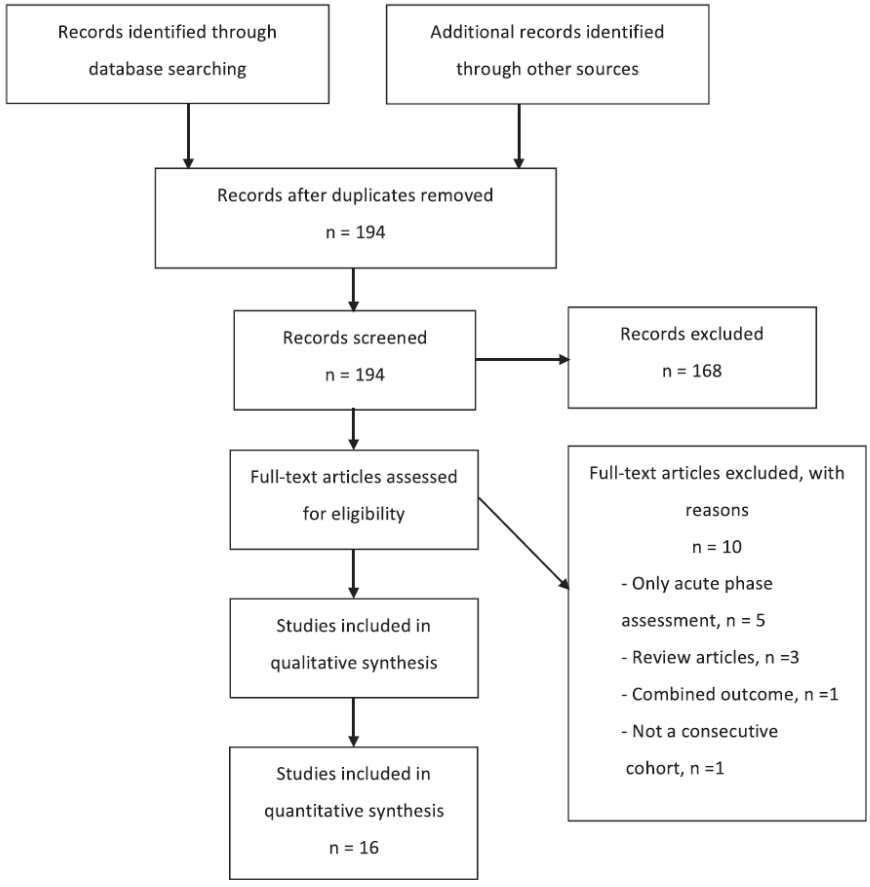
GHRH- arg test: growth hormone releasing hormone plus arginine test, ITT: insulin tolerance test, d: TRH: thyrotropin releasing hormone, ACTH: adrenocorticotropic hormone, LHRH: gonadotropin releasing hormone, lost to FU number: number of patients lost in follow up of studies with more than one measurement overtime.

Results

Selection of studies

Initially, 194 citations (abstracts) were found. Of these citations, 62 articles did not report relevant endocrine outcome. Eighty-eight studies concerned other diseases than aneurysmal SAH. Eighteen case reports were also excluded. Twenty-six full-text articles were collected of which 5 articles reported only early phase endocrine dysfunction [22-26], 3 were review articles [27-29], 1 article reported combined data of SAH with traumatic brain injury [30] and 1 large study was excluded because it concerned an internet based data collection study [31]. Finally sixteen studies fulfilled the inclusion criteria and were eligible for the current review (Figure 1).

Figure 1. Flowchart outlining the selection process of articles according to PRISMA guidelines.



From: Moher D, Liberrati A, Tetzlaff J, Altman DG, The PROSMA Group (2009). Preferred Reporting Items for Systematic and Meta-Analyses: The PROSMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

Study characteristics and methodological quality

Study population size ranged from 10–93 patients. Six studies were cross-sectional or retrospective cohort studies [17,33-36,46]. Ten studies were conducted prospectively [32,37-45]. Interval between SAH and neuroendocrine assessment in studies reporting neuroendocrine outcome ranged from 3 months to 10 years.

Dimopoulou et al. retrospectively analyzed 30 patients between one and two years after SAH but did not use a stimulation test for the evaluation of growth hormone function [17]. Aimaretti et al. conducted a prospective follow-up study of 40 patients after SAH derived from multiple Italian centres. The patients were all conscious and measured 3 months after discharge from the ICU. GHRH + arginine test was used to measure growth hormone function [37]. Aimaretti et al. prospectively studied 32 patients in Italian hospitals, and performed basal hormonal tests and GHRH + arginine test as a dynamic test to establish GHD between 3 and 12 months after SAH [32]. Brandt et al. selected 10 patients with fatigue after SAH and measured corticotrophin, growth hormone and thyrotrophic function using insulin tolerance test (ITT) and TSH-Thyroid releasing hormone stimulation tests12 month after SAH. In 30% of the patients ITT was not performed [33]. Kreitschman-Andermahr et al. retrospectively studied 40 SAH patients from a cohort of 274 patients after excluding patients with liver disease, coronary heart disease, convulsions, DM, depression, severe confusional state or vegetative state after discharge. ITT and THRH-LHRH were used as dynamic tests for assessment of ACTH, TSH and GH function 12 to 72 months after SAH [35]. Kreitschman-Andermahr et al. retrospectively measured basal hormones in 45 patients 3 to 24 moths after SAH. Only 14 patients had dynamic tests [36]. Jovanovic et al. retrospectively evaluated endocrine function in 93 patients, between one and ten years after SAH, however stimulation tests were not used [34]. Tanriverdi et al. prospectively analysed 22 patients one year after SAH using basal and dynamic tests for ACTH and GHD [39]. Karaca et al. did a follow-up study, three years after SAH of 20 patients investigated by Tanriverdi et al. in the abovementioned study using basal hormonal tests and glucagon stimulation test [45]. They found 4 cases of GHD three years after SAH of whom three did not have GHD one year after SAH. Dutta et al. evaluated endocrine function in 60 SAH patients with anterior communicating artery (A-com) and middle cerebral artery (MCA) aneurysms using only basal hormonal tests. Part of the study was retrospective, analysing patients one year after SAH and partly prospectively analysing patients 6 months after SAH [46]. Kronvall et al. prospectively analysed 45 patients in the acute phase and 3 to 6 months after SAH, using basal hormonal test and GHRH-arg test for GHD. They did not use a dynamic test to establish ACTH deficiency [44], Khursheed et al. prospectively analyzed 73 patients nine months after SAH for TSH and gonadotropin deficiency and not the other anterior pituitary hormones [43]. Blijdorp et al. prospectively analysed 84 patients and reported preliminary data of 43 patients using basal hormonal tests, synacten test when ACTH deficiency was suspected and a ghrelin test in the early phase after SAH and confirmatory GHRH-arg test after six months [42]. The most prominent methodological shortcomings were the incomplete reports of

patient selection [17,32,33,35,37,46], selection bias [17,33-35,42,46] and inadequate laboratory testing [17,33,35,36,38,43,44]. Some studies did not use dynamic tests to determine growth hormone or corticotrophin deficiency [17,34,43,44,46]. In some reports, description of the statistical analysis and results were incomplete [36] or even absent [33].

Frequency and type of hypopituitarism after SAH

In total, 671 patients were examined for hypopituitarism after SAH (Table 2). The proportion of patients with endocrine dysfunction varied from 0 - 55%. Growth hormone deficiency occurred in 0 to 29%, adrenocorticotropic deficiency in 0 to 40%, gonadotropin (luteinizing hormone, follicle stimulating hormone and testosterone) deficiency in 0 to 40% and thyroid stimulating hormone deficiency in 0 to 20% of patients in different studies. The largest prospective study by Klose et al. evaluated 62 patients for an average of 14 months (range 11–26 months) after SAH. Although they found some evidence of hypopituitarism after initial testing, they were not able to confirm hypopituitarism by confirmatory laboratory tests. They found no evidence of hypopituitarism in the long term after SAH [40]. In another well designed study, two different confirmatory tests were used to establish GHD adjusting the outcome for body-mass index [41]. After 12 months, 12% of the patients had pituitary dysfunction (PD).

Predictors for hypopituitarism after SAH

Inconsistent results for predicting hypopituitarism after SAH were reported. In a series of 93 patients with SAH, cerebral vasospasm and hydrocephalus were identified as risk factors for pituitary dysfunction [34]. Kreitschmann-Andermahr et al. found a significant association of female sex and the presence of corticotrophin deficiency [35]. Kronvall et al. reported that younger age was significantly associated with pituitary dysfunction at follow-up [44] but Tanriverdi et al. found higher age to be associated with growth hormone deficiency in the acute phase after SAH [39]. These findings were not confirmed by other studies [17,32,40,47].

Association between hypopituitarism after SAH and functional recovery

In a series of 26 patients, 14 (54%) had neuropsychological deficits, but only 1 patient suffered neuroendocrine dysfunction at six months after SAH [38]. A study of 40 patients evaluated the effect of neuroendocrine dysfunction on quality of life and psychiatric symptoms. Low basal cortisol level was associated with low quality of life scores and high depression scores [48]. Severe GH deficiency was associated with low scores on the energy subscale of Nottingham Health Profile (NHP) questionnaire. Gardner et al. did not find an association between PD and quality of life after SAH, measured using the quality of life in adult GHD assessment (QOL-AGHDA) [41].

Table 2. Summary of studies assessing frequency of pituitary deficiency after SAH

Study	Time after SAH (months)	Patients n	GH%	ACTH%	TSH%	LH/FSH%	Testosterone%	Multiple%	Total%
Aimaretti et al. [37]	3	40	25	2.5	7.5	12.5	*	10	37.5
Brandt et al. [33]	12	10	10	0	20	10	30	30	30
Dimopoulou et al. [17]	12-24	30	37	10**	7***	13	*	13	47
Kreitschmann-Andermahr et al. [35]	12-66	40	20	40	4	0	0	12	55
Aimaretti et al. [32]	12	32	21.8	6.25	9	3	3	6	37.5
Kreitschmann-Andermahr et al. [36]	3-24	45	8	13	0	0	0	9	13
Jovanovic et al. [34]	12-120	93	29	22	2.5	7.5	*	7.5	49.5
Lammert et al. [38]	6	26	0	0	4	0	0	0	4
Tanriverdi et al. [39]	12	22	36	14	0	0	0	4	50
Klose et al. [40]	12-24	62	0	0	0	0	0	0	0
Gardner et al. [41]	12	50	10	2	0	0	0	0	12
Dutta et al. [47]	6	60	15	2	13	13	23	6	31.6
Kronvall et al. [44]	3-6	45	7	18	2	4	*	NR	27
Khursheed et al. [43]	9	73	NR	NR	3	0	0	0	3
Karaca et al. [45]	36	20	20	0	0	0	0	0	20
Blijdorp et al. [42]	6	43	14	0	0	28	*	7	30

Abbreviations: n: numbers,%: percentage; FSH: follicle-stimulating hormone; LH: luteinizing hormone; TSH: thyroid-stimulating hormone; GH: growth hormone; ACTH: adrenocorticotropic hormone; NR: not reported; *: reporting LH, FSH and testosterone together as gonadotropin deficient; **: ACTH hypo-responsive; ***: subclinical TSH deficient.

Discussion

From the 16 studies we evaluated in this review, 15 showed some evidence for neuroendocrine dysfunction on one or more pituitary axes in the long term after SAH. In one study neuroendocrine dysfunction was only present in part of the patients in the early phase and not in the long-term after SAH. Most frequently, growth hormone deficiency was found, subsequently followed by adrenocorticotropic deficiency, gonadotropic deficiency and TSH deficiency. The reported prevalence of hypopituitarism varied from 0 to 55%. Single hormone deficiencies, mainly GHD, were more frequently found than multiple hormone deficiencies. The axes that were affected also varied among different studies.

Several mechanisms may lead to altered pituitary function in patients with SAH. Endocrine dysfunction may be provoked by compression of the hypothalamic-pituitary complex by the aneurysm itself, post-haemorrhagic local tissue pressure changes, toxic effects of extravasated blood, ischemia caused by vasospasm, increased intracranial pressure, hydrocephalus, or local destruction during craniotomy. The pituitary gland is divided into an anterior and posterior lobe. The anterior lobe is responsible for producing several peptide hormones: ACTH, TSH, prolactin, GH and gonadotropin hormones: LH and FSH. The posterior pituitary is a storage organ for the ADH and oxytocin [19]. The pituitary gland is supplied with blood from the branches of the internal carotid artery, which form a capillary plexus in the region of the median eminence of the hypothalamus. Blood from this area reaches the anterior pituitary by means of long and short portal veins through the pituitary stalk. The middle and inferior hypophyseal arteries supply the pituitary stalk and neurohypophysis with arterial blood [19]. This difference in blood supply might play a role in the pathophysiology of endocrine dysfunction after SAH, because it is the anterior pituitary hormones that are more often affected after SAH. Nevertheless, posterior pituitary can also be affected. Hyponatremia is a common symptom in the early phase of SAH [49]. The exact mechanism of this complication after SAH is still poorly understood. There are different theories about the cause of this symptom. Different study groups have suggested syndrome of inappropriate antidiuretic hormone secretion as the main cause of hyponatremia after SAH [50,51]. Yet others have suggested cerebral salt wasting syndrome due to the rise of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) together with volume depletion through ADH hypo-secretion [52-56]. Furthermore, due to the presence of ACTH deficiency in the early phase after SAH [40,25], ACTH deficiency has also been mentioned as one of the possible mechanisms for developing hyponatremia. Clinical evidence for this theory is lacking and needs further evaluation [51]. Intriguingly, single deficiencies were more often described than multiple hormonal deficiencies. This may imply that specific parts or systems of the anterior lobe of the pituitary gland are more vulnerable to damage than others. On the other hand, the single anterior pituitary axis deficiencies may be a marker of multiple deficiencies, which are not detected due to inappropriate testing.

The inconsistent results of the studies may be explained by differences in patient selection, time elapsed between SAH and endocrine evaluation, and different methodology of endocrine tests and definitions of hypopituitarism between the studies. Some studies were cross-sectional or retrospective studies [17,33-37,57] which are likely to be affected by selection bias, misclassification or information bias. Prospective cohort studies are best qualified in determining the occurrence of hypopituitarism after SAH. Patient selection may still be a problem in these studies [32,37,38]. There were large differences in time elapsed between SAH and the evaluation of endocrine function after SAH between studies [34,35,37,38] and even within studies [34-36]. The association between SAH and hypopituitarism could be affected by the time elapsed between SAH and the laboratory testing.

Another concern is the definition of hypopituitarism and methods used to measure endocrine function. In clinical practice and in clinical research it is difficult to define and operationalize hypopituitarism. Specific endocrine testing for each pituitary function must be performed to set an accurate diagnosis. The evaluation of pituitary function is preferably done according to an algorithm, which is interpreted by an endocrinologist in collaboration with a multidisciplinary team responsible for the patient [58]. Basal concentrations alone are not always distinctive, because of pulsatile, circadian or situational secretion. This may have led to misinterpretations of hormone values in some of the studies [17,34,46]. The assessment of ACTH and GH requires dynamic tests to reliably detect deficiency of these hormones [19]. Dynamic tests were not performed in three of the studies [17,34,46] and in some studies the tests conducted even varied within the cohort [33,36,38].

Even when dynamic tests were used validation of some of the tests such as insulin tolerance test, thyrotropin releasing hormone and adrenocorticotropic hormone stimulation test in SAH patients remains a concern [59-62]. Furthermore, the GHRH-arg test is strongly influenced by body mass index (BMI). Outcomes of GHD should be adjusted for BMI, which was not the case in various studies [32,37,39]. There is a lack of standardized tests, which makes it difficult to interpret the findings of some studies. Based on these shortcomings PD after SAH might have been over-reported in older studies [32].

Despite all shortcomings of the reviewed literature, there seems to be at least some preliminary evidence that pituitary dysfunction is associated with SAH. Younger age was associated with long-term pituitary dysfunction in one study and hydrocephalus and vasospasm was associated with pituitary dysfunction in another [34,44]. However, due to the relatively small number of patients [44] and methodological shortcomings of the studies as we mentioned earlier (case series with a time range between 1 and 10 years without pre-trial registry and no dynamic tests) [34], the role of these factors remains unclear. Still there are a few studies with a proper methodological set up and implementation but the number of cases remains small and the studies show widely diverging results [39-41].

In general, patients with hypopituitarism may have many different symptoms, including for instance fatigue, impairment of concentration, infertility, weight gain and hair loss. For clinicians, it might be efficient to use the clinical symptoms of hypopituitarism to select patients for further endocrine evaluation. However the symptoms are non-specific and do not indicate the presence or type of endocrine dysfunction accurately. In a study in which patients were selected for endocrine evaluation based on clinical symptoms of hypopituitarism [33], the reported prevalence of pituitary dysfunction was approximately 30%. This is in accordance with other studies, in which patients were not selected based on symptoms. This suggests that selection based on clinical symptoms is not efficient. On the other hand there is insufficient evidence to support routine assessment of pituitary function in all SAH patients, because the clinical relevance of pituitary dysfunction after SAH is largely unclear [63].

There were no studies reporting functional long-term outcome in association with endocrine function after SAH. In addition, we could not identify any studies that evaluated the effect of hormone substitution on any of the clinical symptoms in patients with SAH. Interestingly, there are no proper case–control designed studies answering the question whether SAH is a risk factor for the development of hypopituitarism. Such studies should have a case control design and involve a large study population, and should therefore probably be based on hospital registries. Such studies would provide a sound basis for further scientific explorations of the occurrence and risk factors for hypopituitarism after SAH.

Conclusions

In conclusion, SAH seems to be associated with increased risk of endocrine dysfunction. Currently, there are no neurological or clinical parameters predicting the presence of hypopituitarism after SAH. Whether detection and possible treatment of endocrine dysfunction after SAH leads to better functional recovery is also unknown. Large prospective studies are needed to more precisely assess its effect on mood, behaviour and quality of life.

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3

Chapter 3

Diagnostic value of a ghrelin test for the diagnosis of growth hormone deficiency after subarachnoid hemorrhage

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Abstract

Objective: To determine the diagnostic value of a ghrelin test in the diagnosis of growth hormone deficiency (GHD) shortly after aneurysmal subarachnoid hemorrhage (SAH).

Design: Prospective single-centre observational cohort study

Methods: A ghrelin test was assessed after the acute phase of SAH and a growth hormone releasing hormone (GHRH) arginine test 6 months post SAH. Primary outcome was the diagnostic value of a ghrelin test as compared to the GHRH arginine test in the diagnosis of GHD. The secondary outcome was to assess the safety of the ghrelin test, including patients' comfort, adverse events and idiosyncratic reactions.

Results: Forty-three survivors of SAH were included (15 male, 35%, mean age 56.6 ± 11.7).

Six out of 43 (14%) SAH survivors were diagnosed with GHD by GHRH arginine test. In GHD subjects, median GH peak during ghrelin test was significantly lower than non-GHD subjects (5.4 versus 16.6 p=0.002). ROC analysis showed an area under the curve of 0.869. A cut-off limit of a GH peak of 15 μg/L corresponded with a sensitivity of 100 % and a false positive rate of 40%. No adverse events or idiosyncratic reactions were observed in subjects undergoing a ghrelin test, except for one subject who reported flushing shortly after ghrelin infusion.

Conclusion: Due to its convenience, validity and safety, the ghrelin test might be a valuable GH provocative test, especially in the early phase of SAH.

Introduction

The incidence of spontaneous subarachnoid hemorrhage (SAH) in the Netherlands varies between 5.7 per 100,000 subjects per year for men and 9.9 per 100,000 subjects per year for women. About 50 percent of SAH patients do not survive [1, 2]. Those who do survive SAH have high rates of functional limitations that could lead to impaired quality of life, fatigue, decreased mobility, and loss of motivation. These symptoms could be caused by growth hormone deficiency (GHD)[1, 3]

The prevalence of hypopituitarism after SAH varies between 0 and 55%, with GHD in 0-29%, being the largest deficit among all SAH patients [3-12]. This neuro-endocrine dysfunction may result from the hypothalamic/pituitary system being damaged as a result of post hemorrhagic complications, e.g. local tissue pressure, toxic effects of the extravasated blood, ischemia, hydrocephalus or local destruction during cerebral surgery.

GHD is diagnosed with a dynamic stimulatory test, as standard serum insulin-like growth factor I (IGF-I) tests cannot discriminate between sufficient and insufficient growth hormone secretion [13]. Currently, the gold standard for the diagnosis of GHD is the insulin tolerance test. Since this test is contra-indicated in the elderly and in patients with ischemic heart disease and seizures, it is regularly replaced by the GHRH arginine test, which is well-validated in adults [13]. However since both tests are burdensome and limited by side effects such as vasodilatation and paresthesia[14], they are not useful in the early phase after SAH where these side effect might be confused with complications of SAH such as delayed cerebral ischemia which need proper treatment.

It might be possible to diagnose GHD occurring shortly after SAH by combining early hormonal screening with GH stimulation testing. By its binding to the GH secretagogue receptor type 1a, ghrelin has a strong GH releasing activity, and can be used as diagnostic test. A ghrelin test is not limited by side effects and it has the advantage of also stimulating adrenocorticotrophin (ACTH)[15]. As there is little data describing the use of ghrelin as a GH stimulating diagnostic test, the aim was to determine the diagnostic value of a ghrelin test shortly after SAH to identify subjects with GHD and to define the cut-off limit of the GH peak below which GHD is confirmed.

Methods

Study Design

This study was part of the HIPSS (Hypopituitarism in patients after subarachnoid hemorrhage study), a prospective single-centre observational cohort study at the Erasmus University Medical Center Rotterdam. It was approved by the local medical ethical committee (METC). All patients gave written informed consent. Adverse events were registered and reported to the Central Committee for human scientific research (CCMO).

Subjects

Included in this study were all patients with aneurysmal subarachnoid hemorrhage, aged ≥ 18 years. All patients included in this study were treated for SAH before inclusion. They were dismissed from the intensive care unit and admitted to the department of neurology of the Erasmus MC between June 2009 and June 2012. We excluded patients with any hypothalamic/pituitary disease, former cranial irradiation, prior significant head trauma or any other medical condition or laboratory abnormality that may have interfered with the outcome of the study.

Clinical definitions & Outcome measures

The primary outcome was to compare the ghrelin test with the GHRH arginine test in terms of their value for the diagnosis of GHD. The secondary outcome was to assess the safety of the ghrelin test, including patients' comfort, adverse events and idiosyncratic reactions.

The diagnosis of subarachnoid hemorrhage (SAH) was confirmed by computerized tomography (CT) or lumbar puncture. Localization of the aneurysm was determined by CT angiography or a digital subtraction angiography. We defined growth hormone deficiency (GHD) as an insufficient growth hormone response to a GHRH arginine test, assessed at six months after SAH. We used the following cut-off limits to define GHD for the GHRH arginine test: for subjects with a body mass index (BMI) < 25 kg/m2, a peak GH <11 μg/L; for subjects with a BMI between 25 and 30 kg/m2, a peak GH <8 μg/L; and for subjects with a BMI > 30 kg/m2, a peak GH <4 μg/L [13].

To rule out interference of other hormonal deficiencies, we simultaneously measured basal hormone levels including cortisol, free thyroxin (fT4), thyroid-stimulating hormone (TSH), prolactin, insulin-like growth factor-1 (IGF-1), and insulin-like growth factor binding protein3 (IGF-BP3), in men and women, testosterone in men, an d estradiol, follicle stimulating hormone (FSH), and luteinizing hormone (LH) in women. IGF-1 was assessed by immulite 2000 (DPC Biermann GmbH/Siemens, Fernwald, Germany), a solid-phase, enzyme-labeled chemiluminescent immunometric assay, with an intra assay variability of 2-5%, and an inter assay variability of 3-7%16, we calculated IGF-1 mean standard deviation score (SDS)[17]. IGF-1 are depicted in table 1.

Acute phase

A ghrelin test was assessed in a fasting patient at rest, during admission after SAH. Body mass index (BMI) was calculated from height and body weight [18]. At baseline, we measured GH and cortisol, and then infused 1 μg per kg body weight acylated ghrelin. GH and cortisol were measured after 30 and 60 minutes. A recent study showed that individual peak GH response to ghrelin occurred in all subjects between 15 and 45 minutes with a curve maximum at 30 minutes after ghrelin test, in GHD and non-GHD patients[19].

Six months post-SAH

A GHRH arginine test was assessed at the research unit 6 months after SAH. GH was measured, followed by infusion of 1 microgram/kg body weight GHRH and 0.5 mg / kg arginine within 30 minutes. Every 5-15 minutes GH was assessed.

Statistical analysis

Data were expressed as mean ± standard deviation for normal distributed variables or as median (ranges) for non normative variables. To evaluate differences in GH peak between GHD and non GHD subject, Mann-Whitney U test was assessed. To determine the value of applying a ghrelin test shortly after SAH to identify subjects with GHD, the sensitivity, specificity, and positive and negative predictive values were calculated using Receiver Operating Characteristics (ROC analysis). The reference test for detection of GHD is the GHRH arginine test. In addition, the likelihood ratios of a positive ghrelin test and of a negative ghrelin test were calculated. All statistical analyses were performed with SPSS version 20.0 (SPSS Inc. Chicago, Illinois, USA).

Results

Patients

Out of 241 patients admitted to the ICU with the diagnosis of SAH, 193 survived. Fifty-one patients did not fulfill the inclusion criteria, 38 refused to participate and 20 patients were discharged before inclusion was fulfilled. Eventually, 84 patients were included in the HIPSS study (Figure 1). Fifteen patients had a ghrelin test and no GHRH-arg. They found the endurance of the dynamic tests too strenuous. At the start of the study, ghrelin test was not at our disposal; so 10 patients only had a GHRH-arg test but no ghrelin test. 16 patients did not give us permission to perform dynamic tests.

In 43 patients, both the ghrelin test and the GHRH arginine test were assessed and therefore data of 43 patients was analyzed in the current study. Patient characteristics are outlined in Table 1. Median time between occurrence of SAH and ghrelin test was 18 days. Patient characteristics of excluded subjects, and included patients did not differ significantly (male sex 9/41 (22%) versus 15/43 (35%) p= 0.142, mean age 56.3 versus 56.6 years, p=0.912).

Outcome

Six out of 43 (14%) SAH survivors were diagnosed with growth hormone deficiency by GHRH arginine test. The median GH peak of GHD subjects was 5.4 μg/L during the ghrelin test and 6.2 μg/L during the GHRH arginine test (Figure 2). In GHD subjects, median GH peak during ghrelin test was significantly lower than non-GHD subjects (5.4 (range 1.6-14.6) versus 16.6 (4.1-117) p=0.002). We observed a low cortisol level in one patient (2%) during ghrelin testing. This subject was re-tested using the synacten-test did not reveal a secondary hypocortisolaemia. Three male patients with

GHD also had a hypogonadotropic hypogonadism. Another 9 patients in this study had hypogonadotropic hypogonadism after six month.

ROC analysis showed an area under the curve of 0.869. Table 2 gives an overview of sensitivity, specificity, positive predictive value and negative predictive value for different cut-off limits of the GH peak during a ghrelin test. A sensitivity of 100%, which is needed to diagnose every GHD subject, gives a false positive rate of 40% (1-specificity), belonging to a cut-off of 15 µg/L (Table 3). A cut-off of 11.4 µg/L gives the optimal combination of the highest sensitivity (83%) and the highest specificity (73%).

Adverse events / Safety measures

Only one subject reported an adverse effect, i.e. flushing starting shortly after ghrelin infusion, which lasted for 30 minutes. During this period we monitored heart frequency and blood pressure, which remained stable. No adverse events or idiosyncratic reactions were reported by or observed in the other subjects undergoing a ghrelin test.

Discussion

Ghrelin testing is a safe and valid alternative in the diagnosis of GHD shortly after SAH. Other current available GH provocative tests might be burdensome and their use is limited in SAH survivors because of their possible side effects.

Ghrelin, a 28-amino-acid peptide hormone, is predominantly produced by the stomach, stimulates food intake and a positive energy balance and plays an important role in fat metabolism [20]. Besides, ghrelin has strong GH releasing activity by binding to the GH secretagogue receptor type 1a (GHSR-1a). Apart from stimulating GH secretion, ghrelin exhibits hypothalamic activities resulting in stimulation of prolactin (PRL) and ACTH secretion[20]. Previous studies described the use of ghrelin as GH stimulation test, when combined with GHRH, illustrating a strong and potent GH releasing activity, due to the synergistic effects of ghrelin and GHRH [21-24]. Additionally, administration of ghrelin alone illustrated a GH release with a clear dose response curve in normal subjects [22, 25]. In GHD subjects, GH response was significantly lower than in normal subjects, illustrating the value of a ghrelin test in diagnosing GHD [24]. The use of GH-releasing peptide-6 (GHRP-6), which is an artificial hexapeptide activating the GHSR-1a, in combination with GHRH, has been described as a potent GH provocative test in several studies investigating pituitary dysfunction after traumatic brain injury [26-28]. In the current study, a ghrelin test was assessed shortly after SAH and illustrated a significantly lower GH peak in GHD subjects compared to non GHD subjects. ROC analysis showed a high accuracy of the ghrelin test when compared with GHRH-arginine test. The GHRH arginine test, however, is inconvenient in SAH patients because of its known side effects such as vasodilatation and paresthesia[14]. A more safe and patient friendly test, like a ghrelin test, would be preferred, especially in disabled patients who are critically ill. Another known side effect of GHRH administration is transient facial flushing, which occurs in 25% of the patients[14]. In our view, this side effect might be

related to fluctuating blood pressure, which is also undesirable in patients in the early phase after SAH.

In a recent paper published by Gasco et al, ghrelin test proved to be a valid diagnostic test for GHD in adults with reliable cut off limits in lean and overweight patients[19]. Furthermore, they concluded that obesity has an impact on the GH response to ghrelin, lowering the predictive value of the test in these patients, so caution must be taken when it comes to interpreting ghrelin test in obese patients. However obesity has an impact on almost all dynamic GHD test[29]. They also described that facial flushing occurred in a smaller group of patients after ghrelin test compared with GHRH arginine test. Other adverse events of ghrelin administration have not been described so far except for patients receiving more than 250 microgram of ghrelin, who reported transient hyperhydrosis [22, 25].

Beside its convenience the ghrelin test would be preferred above the GHRH arginine test since by stimulating adrenocorticotrophin (ACTH) release, adrenal function could be evaluated. The prevalence of adrenocorticotropic deficiency following SAH varies from 0% to 40% [6, 8, 12, 30] and could lead to life-threatening conditions if untreated. This elucidates added value of the ghrelin test since it can be used to detect a secondary adrenocorticotropic deficiency early after SAH. However, since the ACTH releasing activity is less potent, higher ghrelin doses may be needed in order to discriminate between sufficient and insufficient cortisol response [24]. Therefore, the evaluation of adrenal function by ghrelin testing should be elucidated in further studies.

We observed that a second confirmatory test was needed to confirm true GHD in patients who had low GH response to the ghrelin test. A recent study by Gardner et al. also concluded that real GHD in SAH patients has to be confirmed by two different stimulation tests and by application of BMI specific cut-offs[1]. Based on these findings, we recommend the usage of two different stimulation tests for the confirmation of true isolated GHD.

The limitation of this study was that cut-off limits for the ghrelin test could not be defined, since only 6 patients had been diagnosed with GHD. Fortunately the cut off values for ghrelin test were recently published by a different group of investigators[19].

Secondly, the time between GH stimulation tests could be an important confounder since hypopituitarism in the acute phase has been described to resolve in the post-acute phase[11, 32]. This might be caused by the SAH or SAH's related complications. Furthermore the fact that the subjects are critically ill could also have a significant impact on the results of the ghrelin test. However, some studies have shown that in contrast to both hypogonadism and hypocortisolism that can normalize during follow-up, GHD prevalence remained stable until one year after SAH [33, 34]. Ideally, multiple GHD tests in this early phase could exclude these possible confounders, however it is not feasible to perform multiple tests in critically ill SAH patients.

In conclusion, the ghrelin test discriminated between GHD and non-GHD survivors of SAH and displayed a high accuracy as compared with the GHRH arginine test. Due to its convenience, validity and safety, the ghrelin test is a novel GH provocative test that can be used as a screening tool for prediction of late GHD in SAH patients.

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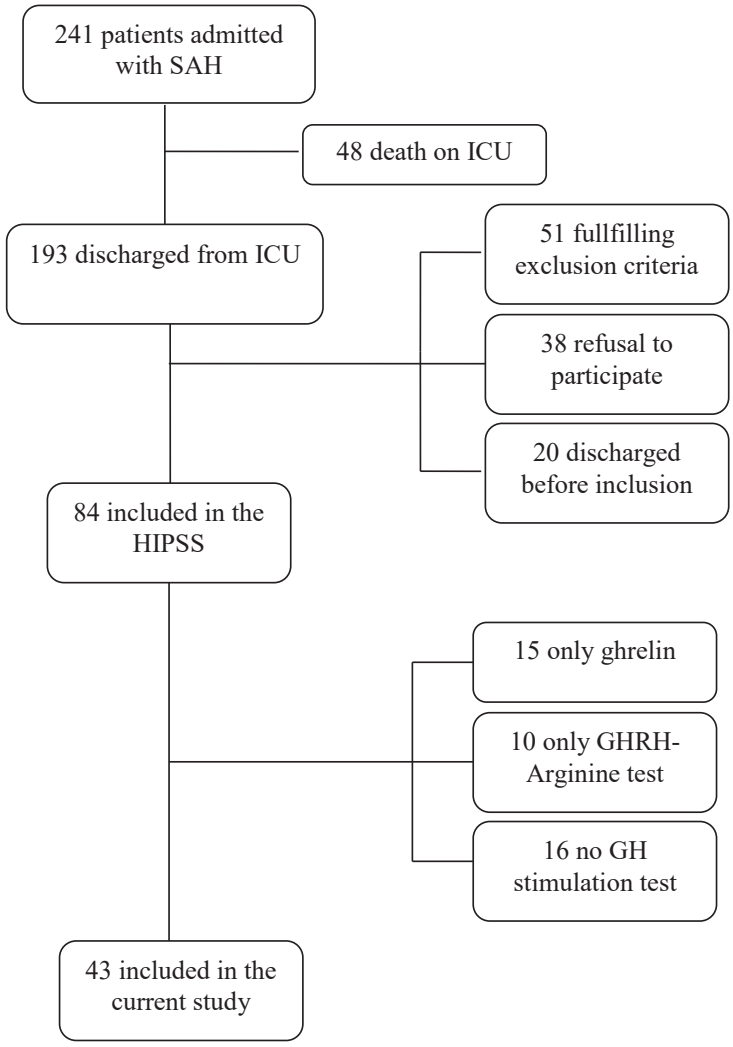
Figure 1. inclusion of subjects



SAH subarachnoid hemorrhage; **ICU** intensive care unit; **GH** growth hormone; **GHRH** growth hormone releasing hormone **HIPSS** hypopituitarism in patients after subarachnoid hemorrhage study

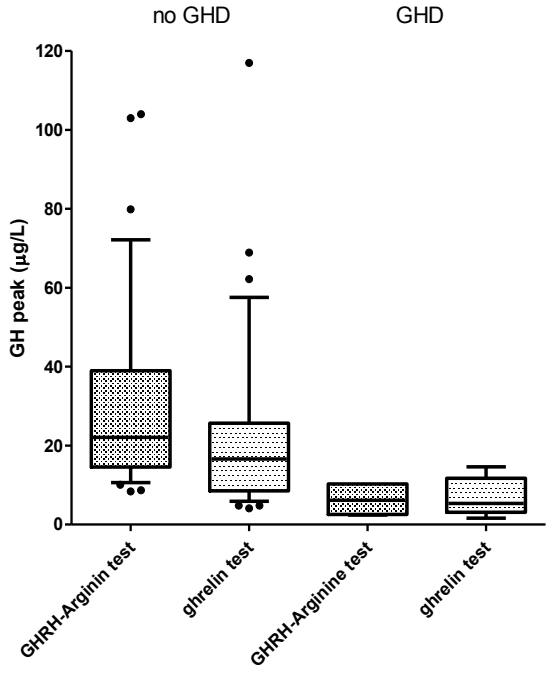
Table 1. baseline characteristics & results of dynamic tests of included and excluded survivors

	SAH patients with ghrelin test and GHRH arginine test (N=43) N	**Excluded SAH patients in the current study (N=41)**
	Values are expressed as number of subjects+	
Sex (male)	15 (35)	9 (22)
Age (years)	56.6 ± 11.7	56.3 ± 11.8
BMI	25.3 ± 3.1	24.8 ± 4.2
BMI <25 kg/m2	22 (51)	23 (56)
BMI 25-30 kg/m2	17 (40)	12 (29)
BMI >30 kg/m2	4 (9)	6 (15)
WFNS		
I	17 (40)	21 (51)
II	15 (35)	10 (24)
III	3 (7)	0
IV	5 (11)	6 (15)
V	3 (7)	4 (10)
Location of aneurysm		
Anterior circulation	24 (56)	25 (61)
Posterior circulation	19 (44)	16 (39)
Aneurysm treatment		
Endovascular treatment	37 (86)	29 (71)
Clipping	6 (14)	11 (27)
None	0	1 (2)
Hydrocephalus	19 (44)	13 (32)
Delayed cerebral ischemia	3 (7)	5 (12)
GH peak ghrelin test (µg/L)	15.3 (1.6-117)*	N=15, 19.3 (8.2-35.4)*
GH response <5 µg/L	6 (14)	0
Baseline IGF-1 SDS (95% CI)	-0.06 (-2.1; 1.94)**	
GH peak GHRH arginine test (µg/L)	18.1 (2.4-104)*	N=10, 23.2 (4.6-114.0)*
Insufficient GH response	6 (14)	2 (5)
Six months IGF-1 SDS (95% CI)	-0.7 (-2.56; 1.16)**	

BMI body mass index; **GH** growth hormone; **GHRH** growth hormone releasing hormone; **SAH** subarachnoid hemorrhage; **WFNS** world federation of neurologic surgeons grading system for subarachnoid haemorrhage scale

*expressed as median (range); ** expressed as mean (95% confidence interval) + Unless otherwise specified.

Figure 2. GH peak in GH deficient subjects versus non-GH deficient subjects



GH growth hormone; **GHRH** growth hormone releasing hormone

Table 2. summary statistics for various GH cut-off values for the ghrelin test predicting growth hormone deficiency.

GH cut-off for ghrelin test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
2.6	17	100	100	88
3.9	33	100	100	90
4.8	50	97	75	92
6.1	67	92	57	94
11.4	83	73	33	96
15.0	100	60	29	100
20.0	100	38	21	100
30.4	100	16	16	100

GH growth hormone; **PPV** positive predictive value; **NPV** negative predictive value


4

Chapter 4

Pituitary dysfunction after aneurysmal subarachnoid hemorrhage: course and clinical predictors *The HIPS study*

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Abstract

Objective: we describe the occurrence and course of anterior pituitary dysfunction (PD) after aneurysmal subarachnoid hemorrhage (SAH), and identify clinical determinants for PD in patients with recent SAH.

Methods: we prospectively collected demographic and clinical parameters of consecutive survivors of SAH and measured fasting state endocrine function at baseline, 6 and 14 months. We included dynamic tests for growth-hormone function. We used logistic regression analysis to compare demographic and clinical characteristics of SAH patients with and without PD.

Results: Eighty-four patients with a mean age of 55.8 (±11.9) were included. Thirty-three patients (39%) had PD in one or more axes at baseline, 22 (26%) after six months and 6 (7%) after fourteen months. Gonadotropin deficiency in 29 (34%) patients and growth hormone deficiency (GHD) in 26 (31%) patients were the most common deficiencies. PD persisted until 14 months in 6 (8%) patients: GHD 5 (6%) patients and gonadotropin deficiency in 4 (5%). Occurrence of a SAH-related complication was associated with PD at baseline (odds-ratio 2.6, CI 2.2-3.0). Hydrocephalus was an independent predictor of PD six months after SAH (odds-ratio 3.3 CI 2.7-3.8). PD was associated with a lower score on health related quality of life at baseline (p=0.06), but not at 6 and 14 months.

Conclusions: almost 40% of SAH survivors have PD. In a small but substantial proportion of patients GHD or gonadotropin deficiency persists overtime. Hydrocephalus is independently associated with PD, six months after SAH.

Introduction

Aneurysmal SAH patients with a seemingly good clinical outcome often complain of fatigue and experience high levels of psychosocial stress.[1] These symptoms may interfere with daily activities and social participation, reducing quality of life in relatively young SAH patients.[2, 3] They resemble the symptoms reported by patients with anterior pituitary dysfunction (PD).[4] PD has been reported in 0 to 55% of SAH survivors.[5-9] The most consistent finding is a high proportion of patients with growth hormone deficiency (GHD).[9-11] However, reported incidences vary between studies and the course of PD after SAH is not well known. PD was found to be transient,[12] but seemed long-lasting in other studies.[13] Increased age, hydrocephalus and vasospasm have been identified as possible predictors for PD after SAH,[7, 9] however others could not confirm this.[6, 13]

The conflicting results may be explained by differences in methodology, study population as well as time since onset of SAH.[5, 7] To evaluate the growth hormone (GH) and adrenocorticotropic releasing hormone (ACTH), most of the studies conducted dynamic tests[9, 11] but some did not.[6, 7] In some studies, patients were selected on the basis of symptoms of fatigue[14] or on location of the aneurysm.[15]

In the Hypopituitarism In Patients with Subarachnoid hemorrhage Study (HIPSS) we prospectively assessed the frequency and course of PD over time, using standardized laboratory tests to evaluate neuro-endocrine function in a Dutch cohort of aneurysmal SAH survivors. In addition we searched for clinical risk factors for hypopituitarism after SAH.

Methods

Study Design

The HIPSS study was a prospective single-center observational cohort study. It was registered and approved by the IRB at Erasmus MC University Medical Center, and registered in the Dutch trial registry (NTR 2085). All patients gave written informed consent. The inclusion and exclusion of subjects are described in detail elsewhere.[16] In short, consecutive patients who survived the acute phase of SAH were asked to participate.

Data collection

We prospectively collected baseline characteristics on all patients, including age, medical history, medication use and cardiovascular risk factors. At admission we noted the following neurological parameters: World Federation of Neurological Surgeons grading scale for SAH patients (WFNS), Glasgow Coma Scale (GCS), radiological severity of SAH[17], aneurysm location and type of intervention.

We recorded SAH related complications consisting of hydrocephalus (HC), rebleeding, vasospasm, delayed cerebral ischemia (DCI), intracerebral hematoma (ICH),

hypertension (HT) and hyponatriemia. Patients with symptomatic HC were all treated either by external ventricular drainage or external lumbar drainage prior to endocrine evaluation.

Clinical definitions & Outcome measures

SAH diagnosis was confirmed by computerized tomography (CT) of the brain and in cases with negative CT, by lumbar puncture. Presence and location of the aneurysm was determined by CT angiography and/or a digital subtraction angiography.

The methods of endocrine testing and definitions of PD have been described in detail elsewhere.[16] In short, at baseline and 6 month after SAH endocrine tests were performed and reviewed by an endocinrologist. Endocrine tests included ghrelin test at baseline and GHRH-arg test six months after SAH, in fasting patients. Fourteen months after SAH, all patients were scheduled for basal hormonal testing. In addition, patients with GHD were scheduled for GHRH-arg test. All basal serum samples were taken during fasting before 09.00h.

ACTH insufficiency was considered if basal cortisol level was <110 nmol/L or if cortisol peak during ghrelin test was <450 nmol/L.[18] Criteria for TSH deficiency were low serum fT4 level (<11 pmol/L) combined with an inadequate thyroid stimulating hormone (TSH) levels. Gonadotropin insufficiency was defined when testosterone ≤10 nmol/L or inadequate LH levels. In post-menopausal women LH was regarded as derogatory when below 15 U/L and / or when follicle-stimulating hormone (FSH) was below 35 U/L. In younger women dependent on the stage of cycle and LH, FSH and E2 the gonadal status was assessed. In case oral contraceptives were used gonadal function could not be assessed. We defined anterior pituitary dysfunction as any of the pituitary axis was considered abnormal.

Health-related quality of life (HRQOL) was assessed using question on life satisfaction modules (QLS^{M}-H), a questionnaire that has been developed to evaluate HRQOL in patients with hypopituitarism, among which patients with adult growth hormone deficiency (GHD).[19]

Statistical analysis

Descriptive statistics were used to describe the prevalence of hypopituitarism after SAH. Cardiovascular risk factors prior to SAH, severity of SAH (WFNS, GCS), the presence of hydrocephalus, hypertension, delayed cerebral ischemia and rebleed were considered as predictors for pituitary dysfunction. Independent sample t-tests were used for continuous variables and Pearson's chi-squared test for categorical variables. Associations of risk factors with PD were expressed as odds ratios with 95% confidence interval (CI). Those with a significance level of $p<0.05$ were entered in a multiple logistic regression model using forward selection to determine the independent predictive value of the parameters. We adjusted for potential confounders such as age and sex. All statistical analyses were performed with SPSS version 20.0 (SPSS Inc. Chicago, Illinois, USA).

Results

Of the 198 patients with SAH who were admitted to the ICU, 48 (24%) died, 38 patients (19%) refused to participate, 20 (10%) were discharged to other hospitals before inclusion and 8 were excluded for various other reasons. In total, 84 patients were included in the study (Figure 1). There were no significant differences in age (p=0.18), sex (p=0.24), GCS on admission (p=0.81) and duration of hospital stay (p=0.53) between the included and excluded patients that survived the acute phase.

The baseline and clinical characteristics are shown in Table 1 and 2. Twenty-eight men (33%) and 56 (67%) women were included. Mean age was 55.7 (±11.9) years. All 84 patients were tested for PD at baseline, 72 (86%) at six months and 68 (81%) patients 14 months after SAH. Fifty-nine patients (71%) also had a ghrelin test at baseline and 54 (65%) patients a GHRH-arginine test six months after SAH. For the first ten patients, ghrelin was not available due to logistic problems. Fifteen patients refused dynamic testing.

Table 1. baseline characteristics of included patients

Characteristics	N 84
Age (mean (SD))	55.7 (11.9)
Male	28 (33%)
History of hypertension	18 (21%)
Body mass index (mean, (SD))	25.3 (3.7)
History of smoking	52 (62%)
History of hypercholesterolemia	15 (18%)
History of diabetes mellitus*	4 (5%)

*All patients had DM type II

During follow-up, five patients died of cardiovascular disease consisting of myocardial infarction and cardiac dysrhythmia. In addition, cerebral infarction occurred in 3 (4%) and myocardial infarction occurred in 2 patients (2%). None of these patients had PD prior to the cardiovascular event. One of the patients with GHD developed prostate carcinoma.

Frequency and course of hypopituitarism

Mean time to baseline evaluation was 32 days. Twenty-nine (34%) patients had gonadotropin insufficiency, 26 (31%) possible GHD, 1 (1%) TSH deficiency and 1 (1%) ACTH insufficiency. All female patients (n=19) with gonadotropin deficiency were post-menopausal (mean age 58±10 years). Thirty-seven (44%) patients were deficient on one or more of the endocrine axes at initial evaluation. In 26 (32%) patients only a single axis was deficient and in 11 (13%) two axes were deficient. It concerned GHD combined with gonadotropin deficiency in all but one patient with combined TSH, gonadotropin deficiency.

Table 2. clinical Characteristics of Included Patients

Clinical characteristics	N 84 (%)
GCS on admission	
13-15	66 (79%)
9-12	11 (13%)
3-8	7 (8%)
WFNS on admission	
Grade I	38 (45%)
Grade II	25 (30%)
Grade III	3 (4%)
Grade IV	11 (13%)
Grade V	7 (8%)
Aneurysm location	
Anterior Circulation	49 (58%)
Posterior Circulation	35 (42%)
Intervention	
Coiling	66 (79%)
Clipping	17 (20%)
None	1 (1%)
Complications	
None	43 (51%)
Hydrocephalus	31 (37%)
Rebleed	2 (2%)
Delayed Cerebral Ischemia	8 (10%)
Intraparenchymal Hematoma	15 (18%)
Intraventricular Hematoma	56 (67%)
Vasospasm	7 (8%)

The frequency and number of affected axes are depicted in Table 3. Twenty-two (26.2%) patients had PD six months after SAH, which consisted of gonadotropin insufficiency (20%), GHD (9.5%) and TSH deficiency (1.2%). All female patients with gonadotropin deficiency were post-menopausal. Four patients had two axes affected consisting of GHD and gonadotropin deficiency in all cases.

Table 3. occurrence of Pituitary Deficiency

Hormone deficiencies	Baseline		6 months follow-up		14 months follow-up	
	N (%)	m/f ratio	N (%)	m/f ratio	N (%)	m/f ratio
Any deficiency	37 (44%)	10/27	22 (26%)	10/12	6 (7%)	5/1
GH deficiency	26 (31%)	7/19	8 (10%)	7/1*	5 (6%)	5/0*
Gonadotropin deficiency	29 (34%)	10/19	17 (20%)	5/12	4 (5%)	3/1
ACTH deficiency	1 (1%)	0/1	-	-	-	-
TSH deficiency	1 (1%)	0/1	-	-	-	-

Number (%) of deficient pituitary axes and male/female ratio of deficient patients at baseline, six-, and 14 months after SAH. *: p<0.001; odds ratio:17.8 after six months

Of the 8 patients with GHD at 6 month, two refused retesting at 14 months. In one patient GH function had recovered, testing negative for GHRH-arginine test. PD was present in 6 (7.2%) patients. Five male patients (84%) had GHD of whom 3 (60%) also had gonadotropin deficiency. One postmenopausal female patient had isolated gonadotropin deficiency. In all other patients, pituitary functions were normal.

Clinical determinants for pituitary dysfunction

Table 4 shows the clinical and radiological characteristics of the SAH patients in relation to the presence or absence of endocrine dysfunction at baseline and after 6 months follow-up.

In univariable analysis, hydrocephalus (OR 3.3, 95% CI 1.2-8.9), GCS <13 on admission (OR 2.79, 95% CI 1.0-8.9), WFNS > 2 on admission (OR 2.9, 95% CI 1.1-8.3) and hypertension after SAH (OR3.2, 95% CI 1.2-8.7) were associated with the occurrence of PD six months after SAH. In a multivariable analysis adjusting for age, gender and hypertension, patients with any SAH-related complication had a significant higher chance of having PD at baseline (OR 2.6, 95% CI 2.2-3.0). Hydrocephalus remained independently associated with hypopituitarism at six months (OR 3.3, 95% CI 2.7- 3.8). Growth hormone deficiency at six month after SAH was associated with male gender (OR 17.8, 95% CI 2.0- 58.9). This association persisted after retesting, 14 months after SAH. We found no association between aneurysm location and pituitary function.

We found a trend (p=0.06) for lower score on the QLS^{M}-H at baseline in patients with PD compared with patients without PD, but this trend was not present anymore after 6 or 14 months.

Table 4. Potential Risk Factors for PD at Baseline and 6 Months after SAH

Clinical characteristics	Baseline		6 months follow-up	
	With PD N = 37	Without PD N = 47	With PD N = 22	Without PD N = 62
Age; mean (SD)	**57.5 (11.9)**	**54.3 (11.8)**	**52.9 (12.0)**	**56.7 (11.8)**
Male	10 (27%)	18 (38%)	10 (45%)	18 (29%)
Days in hospital; mean (SD)	18.4 (8.1)	18.0 (10.9)	19.7 (9.1)	17.7 (9.9)
History of smoking	23 (62%)	29 (62%)	14 (64%)	38 (61%)
History of hypertension	11 (30%)	7 (15%)	6 (27%)	12 (19%)
History of DM	0	4 (9%)	0	4 (6%)
History of hypercholesterolemia	8 (22%)	7 (15%)	2 (9%)	13 (21%)
BMI; mean (SD)	25.5 (4.1)	25.1 (3.4)	25.2 (3.6)	25.3 (3.8)
GCS on admission			*	
13 - 15	27 (73%)	39 (83%)	14 (64%)	52 (84%)
9 - 12	5 (13.5%)	6 (13%)	4 (18%)	7 (11%)
3 - 8	5 (13.5%)	2 (4%)	4 (18%)	3 (5%)
WFNS on admission			*	
Grade I	14 (38%)	24 (51%)	8 (36%)	31 (50%)

Clinical characteristics	Baseline		6 months follow-up	
	With PD N = 37	Without PD N = 47	With PD N = 22	Without PD N = 62
Grade II	11 (30%)	14 (30%)	5 (23%)	20 (32%)
Grade III	2 (5%)	1 (2%)	1 (5%)	2 (3%)
Grade IV	5 (13.5%)	6 (13%)	4 (18%)	7 (11%)
Grade V	5 (13.5%)	2 (4%)	4 (18%)	3 (5%)
Location of aneurysm				
Anterior circulation	17 (46%)	31 (66%)	12 (55%)	37 (60%)
Posterior circulation	20 (54%)	16 (34%)	10 (45%)	25 (40%)
SAH treatment				
Coiling	30 (81%)	36 (77%)	19 (86%)	47 (76%)
Clipping	6 (19%)	11 (23%)	2 (9%)	15 (24%)
Complications	‡			
Any	23(62%)	18(38%)	14(64%)	27(44%)
Hydrocephalus	18 (49%)	13 (28%)	13 (59%)#	18 (29%)
Delayed Cerebral Ischemia	7 (19%)	7 (15%)	3 (14%)	11 (18%)
Rebleed	1 (3%)	1 (2%)	0	2 (3%)
ICH	5 (13.5%)	10 (21%)	3 (14%)	12 (19%)
IVH	26 (70%)	30 (64%)	13 (59%)	43 (69%)
Hypertension after SAH	20 (54%)	29 (62%)	14 (64%)*	22 (35%)

ICH: Intraparenchymal Hematoma; IVH: Intraventricular Hematoma, *: P value < 0.05, # : odds ratio 3.3 (95% CI 2.7- 3.8), ‡: odds ratio 2.6 (95% CI 2.2-3.0).

Discussion

In this prospective observational study 39% of survivors of aneurysmal SAH were deficient in one or more pituitary axes at baseline. PD did not occur during follow-up in patients with normal pituitary function at baseline. PD persisted for 6 months in 26% of patients and for at least 14 months in 7%. Gonadotropin and growth hormone were most often affected. Patients were prone to have PD in the early stage after SAH if they had had any of the well-known complications related to SAH. Hydrocephalus was associated with PD six months after SAH and male sex was associated with persistent GHD.

The prevalence of patients with hypopituitarism after SAH exceeds the prevalence in the normal population.[20] Together with the decrease in PD over time, and the association of PD to SAH-related complications and the severity of SAH symptoms, this supports the evidence for a causal relation between SAH and hypopituitarism.

Gonadotropin and/or growth hormone deficiency occurred more frequently than ACTH or TSH deficiency, which is in accordance with other studies.[5, 9, 21] Because it is the anterior lobe of the pituitary gland that contains predominantly thyrotrope, somatotrope and gonadotrope cells,[22] this observation suggests that this lobe is more vulnerable to damage secondary to SAH. This might be due to differences in the position of the pituitary parts in the skull or to differences in blood supply. Blood is supplied to

the anterior lobe through long pituitary portal vessels, which transcend from above the diaphragma sellae, whereas the blood supply to the remaining part of the pituitary gland is derived form middle and inferior pituitary arteries. [4]

In the majority of patients with PD pituitary function recovered during follow-up, while in a small proportion of patients PD persisted. This has been described in similar studies,[9, 12] and is in accordance with studies that found only low numbers of patients with PD long after SAH.[21, 23] Recent findings suggest that the adult pituitary gland is capable of regeneration after injury,[24] which might explain the recovery of pituitary function in our patients. The low proportion of patients with persistent PD described in our and other recent studies differs strongly from that of the older studies.[5, 6, 11] This is probably explained by methodological differences between the studies. In some studies the tests used for detecting PD were not validated.[11] In other studies GHRH-arginine test outcomes were not adjusted for body mass index (BMI), [10, 13] while obesity is a true confounder of GHRH-arginine test and other dynamic tests, and strongly reduces the accuracy of the GH response.[18, 25, 26] In our study, we used two different dynamic tests to establish GHD, and BMI related cut off points were used in accordance with recent recommendations.[21, 27] Furthermore we retested patients with GHD 14 months after SAH to explore whether GHD was a permanent or a transient phenomenon.

We found an independent association between hydrocephalus and persistent PD. Few studies have evaluated possible clinical determinants of hypopituitarism after SAH. Vasospasm and hydrocephalus were identified as risk factors for pituitary dysfunction in one retrospective study with a non consecutive series of patients without using dynamic tests.[7] Other studies reported an association between female gender and corticotrophin deficiency [11] and between older age and growth hormone deficiency in the acute phase after SAH.[9] We observed that PD or GHD was predominantly present in men, which is in line with a recent study.[21] We did not find an association of PD and the location of the aneurysm which is in line with the results of a recent published study. [15] However numbers were small.

Hydrocephalus might play an important role in altering the pituitary function by increasing the intracranial pressure and altering anatomic configuration, which might lead to damage of the hypothalamic-pituitary complex. We also observed that severity of SAH, expressed, as worse GCS and worse WFNS-scores were associated with hypopituitarism in univariable analysis. Even though these determinants were not significant in multivariable analysis (possibly due to the low number of cases with PD in our study), this adds to the evidence that the pituitary gland is damaged by SAH and its complications. Not many studies describe the association of long-term symptoms as health-related quality of life with the occurrence of PD. In our study, a strong overall association was not present.

Whether SAH patients should be screened for PD is under debate, because clinical significance is not clear. However, there are various other reasons besides the possible

association with long-term symptoms to consider early neuro-endocrine evaluation of SAH patients. Adrenal insufficiency might be life-threatening in the early stressful period after SAH and recent findings suggest that early PD has a negative effect on outcome after SAH. [28] Although we found adrenal insufficiency in only 1 (2%) patient, in other studies the proportion of patients with adrenal insufficiency was higher, up to 40 percent.[9, 11]

Early screening for PD might be beneficial in the long-term after SAH. Symptoms of GHD consist of fatigue, low energy level, and decline in cognitive function such as memory and planning,[4] symptoms often found after SAH.[3, 29] These symptoms might hamper the rehabilitation process. Few studies show a decrease in performance functions and life satisfaction in patients with PD after SAH,[30] but others do not support this.[21, 23]

Our study has several limitations. Not all of our patients had a dynamic test to evaluate GHD. This may have lead to an underestimation of the number of patients with PD. Furthermore; two patients with GHD refused re-evaluation after 14 months. The follow-up period was limited and the possibility of recovery of pituitary function beyond this 14-month period cannot be ruled out.

Another limitation is patient selection. Twenty patients were transferred to other hospital for treatment before inclusion was fulfilled. Furthermore we have chosen to include patients who survived the acute phase of SAH. Our selection was based on the idea that we wanted to investigate the course of hypopituitarism in the long-term survivors. Our results cannot therefore be generalized to all patients with acute SAH.

In conclusion, pituitary dysfunction is an actual complication in SAH survivors. Hydrocephalus after SAH is an independent clinical predictor of long-term hypopituitarism after SAH.

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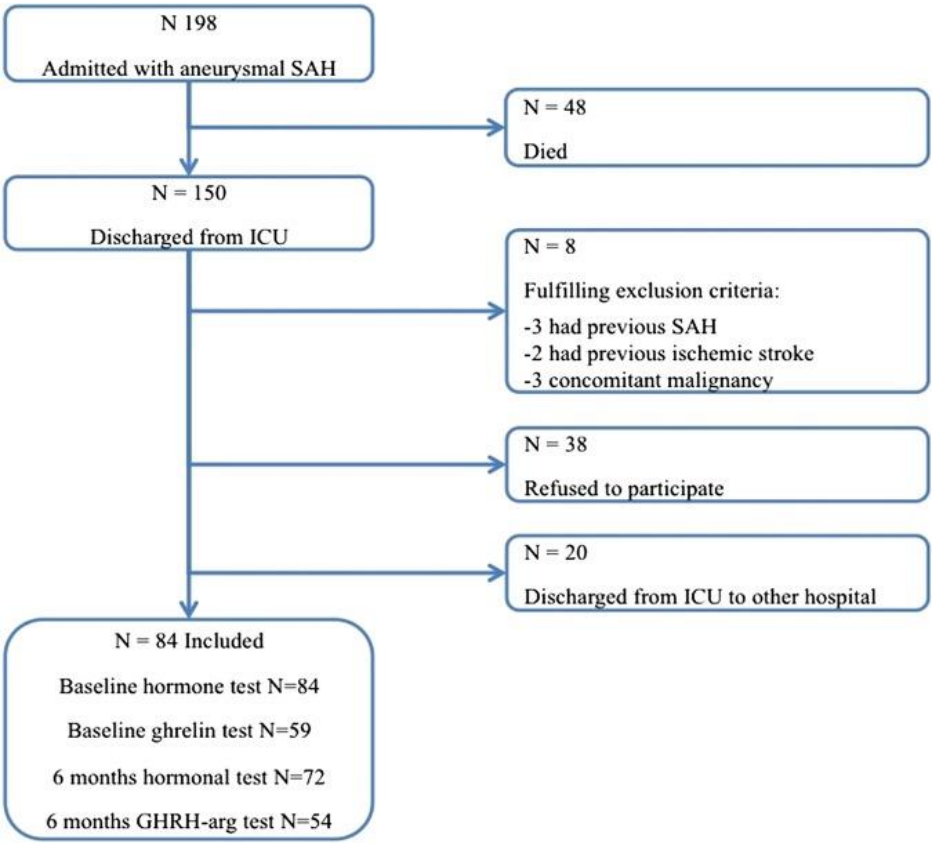
Figure 1. flowchart of patient inclusion.




5

Chapter 5

The effect of hypopituitarism on fatigue after subarachnoid hemorrhage

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Abstract

Background: aneurysmal subarachnoid hemorrhage (SAH) survivors often complain of fatigue, which is disabling. Fatigue is also a common symptom of pituitary dysfunction (PD), in particular in patients with growth hormone deficiency (GHD). A possible association between fatigue after SAH and long-term pituitary deficiency in SAH survivors has not yet been established.

Methods: we conducted a single center observational study among 84 aneurysmal SAH survivors to study the relationship between PD and fatigue over time after SAH, using mixed model analysis. We measured fatigue with the Fatigue Severity Scale (FSS) and studied its relationships with other clinical variables.

Results: three quarter of respondents (76%) have pathological fatigue directly after SAH and almost two third (60%) of patients still have pathological levels of fatigue after 14 months. Severity of SAH measured with World Federation of Neurosurgical Societies (WFNS) score higher than 1 (p=0.008) was associated with long-term fatigue. There is no statistically significant effect of PD (p=0.8) or GHD (p=0.23) on fatigue in SAH survivors over time.

Conclusions: fatigue is a common symptom among SAH survivors. WFNS is a usable clinical determinant of fatigue in SAH survivors. Neither PD nor GHD have a significant effect on long-term fatigue after SAH.

Introduction

Survivors of aneurysmal subarachnoid hemorrhage (SAH) often experience a high level of fatigue in everyday life(1). Fatigue after exertion is a normal response and can be ameliorated by rest. Pathological fatigue is characterized by weariness unrelated to previous exertion and is usually not ameliorated by rest(2).

In SAH patients, pathological fatigue is associated with diminished quality of life and decline in participation in daily activities such as returning to previous work.(3) Anxiety, depression, sleep disturbance and passive coping mechanism have been associated with fatigue after SAH.(4, 5) However the pathophysiological mechanism of fatigue after SAH remains unclear. To our knowledge only one study has evaluated clinical determinants of fatigue after SAH(4) and so far, no clinical predictors have been identified.

PD is a complication of SAH.(6, 7) Depending on the pituitary axis that is affected, patients may experience different clinical symptoms. Growth hormone deficiency (GHD) was found to occur frequently after SAH in some studies.(6, 8) It is well known that chronic growth hormone deficiency leads to fatigue, decreased quality of life, and impairment of attention and memory.(9) One may speculate that GHD is one of the causal factors of fatigue after SAH.

Two studies suggested a possible relationship between fatigue and PD after SAH.(10, 11) However, these studies comprised 10 and 16 patients respectively, and were too small to lead to robust conclusions.

We therefore investigated the association between fatigue and PD after SAH in a cohort of 84 SAH patients. In addition, we aimed to identify clinical predictors of persistent fatigue after SAH.

Methods

Clinical definitions

Our methods, clinical definitions of SAH and data collection have previously been published(12) and the same counts for the methodology and cut-off values of endocrine evaluations. In short, endocrine evaluation was performed in fasting patients between 7:30 and 8:30 in the morning by the endocrinologists and consisted of: cortisol, free thyroxin (fT4), thyroid-stimulating hormone (TSH), prolactin, insulin-like growth factor-1 (IGF-1), and insulin-like growth factor binding protein3 (IGF-BP3), follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone in men, and estradiol in women. To evaluate GHD, a ghrelin test was conducted at baseline, and a confirmatory Growth hormone releasing hormone (GHRH) arginine test was performed at the research unit 6 months after SAH. Metyrapone stimulation test was performed if the basal cortisol level were derogatory or when results from the ghrelin test pointed towards a secondary adrenal insufficiency.(13)

Pituitary dysfunction was defined as an abnormal test value on any of the pituitary axes in the SAH survivors. We defined growth hormone deficiency as an insufficient growth hormone response to a GHRH arginine test, assessed at six months after SAH.

Fatigue was measured with the Fatigue Severity Scale (FSS), which has been validated for healthy subjects and in patients with multiple sclerosis, ischemic stroke, and sleep-wake disorders.(14, 15) The FSS is a self-administered questionnaire with 9 different questions, where each item is scored on a 7-point Likert scale ranging from 1 ("strongly disagree") to 7 ("strongly agree"), concerning fatigue in different situations in the week prior to administration. In accordance with previous studies, a mean score ≥ 4 was considered pathological. The means of the FSS sumscore (sum of all the items on the questionnaire) and the mean score of the individual items were noted along with the standard deviations (SD).(15) All patients were asked to fill out the questionnaire at discharge, at 6 months and 14 months after SAH.

The patients in this study were participants of the hypopituitarism in patients with subarachnoid hemorrhage; screening and treatment (HIPS study), a prospective single-center observational cohort study. It was registered and approved by the IRB at Erasmus MC University Medical Center, and registered in the Dutch trial registry (NTR 2085). All participants gave written informed consent. Adverse events were registered and reported to the Central Committee for human scientific research (CCMO).

Statistical analysis

We studied the possible relation between PD or GHD and level of fatigue over time using linear mixed model analysis with repeated measurements, taking into account that multiple measurements within patients are correlated. This method is very flexible in handling missing measurements by estimating the covariance structure of the data. We used a first-order autoregressive covariance matrix, assuming that measurements closer in time are more correlated than measurements further apart. First, we studied the course of fatigue of the total group over time, entering the FSS scores as dependent variable and measurement time as independent factor. In post-hoc analyses the differences between the 3 time points were studied with Bonferroni correction for multiple comparisons. We repeated this analysis in patients with and without PD or GHD in separate models, studying the patterns of FSS over time within these groups. Finally, we studied differences between the groups by including measurement time, presence of PD or GHD, and the interaction between these two variables (group* time) in multivariable mixed models(16). The interaction term indicates whether the patterns over time differ significantly between patients with and without PD or GHD.

In the same way, we studied relationships of other clinical parameters with fatigue over time, i.e. age, gender, body mass index; severity of SAH (WFNS), the occurrence of hydrocephalus, vasospasm, delayed cerebral ischemia, intraventricular hemorrhage, intra-parenchymal hemorrhage and re-bleed. WFNS was dichotomized in WFNS=1 versus WFNS >1. All statistical analyses were performed with SPSS version 20.0 (SPSS Inc. Chicago, Illinois, USA).

Results

We included 84 patients in this study (figure 1). During follow-up, five patients died of cardiovascular disease (myocardial infarction (n=3) and cardiac dysrhythmia (n=2)). Of the 79 survivors, three had a cerebral infarction, two a myocardial infarction and one patient developed carcinoma of the prostate. A total of 70 patients completed at least one FSS questionnaire during the study; 47 patients at baseline, 60 patients after six months and 52 patients after 14 months. All FSS data of all patients were analyzed. Baseline characteristics of all patients are presented in Table 1. There were no significant differences in baseline characteristics of patients with PD or GHD and patients without PD or GHD.

Level of fatigue after SAH

The mean score of FSS (mFSS) measured over time declined significantly from 4.9 ±1.4 to 4.2 ±1.6 ($p<0.004$) after 6 months. There was no significant change in level of fatigue between 6 and 14 months after SAH (mFSS score 4.3 ±1.7; p=0.9). Seventy-six percent of respondents suffered from pathological levels of fatigue (mean score of FSS ≥4) after discharge (table2). Although there was a decline in number of respondents with pathological level of fatigue to 50% after six months, the number stabilized over time, with 60% of respondents suffering from a pathological level of fatigue 14 months after SAH.

Fatigue and pituitary deficiency

Occurrence and course of PD after SAH in the present study have been described elsewhere(13). Eight respondents with PD in our study suffered from GHD. Secondary hypogonadism was present in 17 patients, consisting of 5 men with testosterone deficiency and 12 postmenopausal women. Four patients had two affected axes consisting of growth hormone deficiency and gonadotropin deficiency.

The difference between patients with PD and patients without PD over time was not statistically significant (interaction group*time, p=0.8). We observed a decline in level of fatigue over time within patients without PD (p=0.009, N= 50). mFSS declined with 0.7 points from baseline (mFSS 4.9±0.45) to 4.2±0.48 at 6 months (p=0.008) and stabilized up to the final measurement at 14 months (mFSS=4.1±0.6, p=1.00). The level of fatigue within patients with PD (n=20) did not change over time (mFSS score: 4.9±0.8 at baseline, mFSS score 4.5±0.8 at 6 months; mFSS score at 14 months 4.6±0.8; p=0.8) (Figure 2).

The changes over time between patients with GHD and patients without GHD were not significantly different (interaction group*time, p=0.23). Analysis within patients without GHD, showed a decline of the level of fatigue over time (p=0.007, N= 42). From baseline (mFSS=4.9±0.6) to 6 months (mFSS=3.9±0.5) the mFSS score decreased 0.9 points (p=0.005), and thereafter remained stable until 14 months (mFSS=4.2±0.6, p=1.00). In contrast, the level of fatigue in patients with GHD (n=8) did not change

over time (mFSS scores: 4.5±1.3, p=1.00) to 6 months (mFSS score 4.7±1.2) and thereafter (mFSS score 4.9±1.2) (Figure 3).

Other clinical predictors of persistent fatigue

Patients with WFNS score of 1 had significantly lower FSS scores (p=0.008). From baseline (mFSS=4.6±0.6) to 6 months (mFSS=3.6±0.6) the mFSS score decreased 1.0 points and remained stable until 14 months (mFSS= 3.7±0.6). The mFSS of fatigue in patients with WFNS score >1 changed from 5.2±0.6, to 4.8±0.5 after six months and to 4.7±0.5 after 14 months (Figure 4). The changes over time between the two groups were not significantly different (interaction group*time, p=0.325). This relation did not change over time (p=0.325) where patients with WFNS 1 score remained significantly lower on mFSS than those with a score higher than 1. All other clinical characteristics were not predictive of persistent fatigue.

Discussion

We found a pathological level of fatigue in three quarter of patients who survived SAH. Although we observed some decline in number of patients with pathological level of fatigue over time, the proportion of patients with pathological fatigue remained high (60%) even after 14 months. Our results are in accordance with other studies showing high levels of fatigue in a large proportion of subjects after SAH.(4, 17)

The cause of fatigue after SAH is not clear. The high prevalence of fatigue shortly after SAH with a decline in the following months, indicates a causal relation between disease or it´s complications and fatigue. The association of pathological fatigue with severity of disease measured by high WFNS on admission, which we have found, adds to this notion. Comparable increased levels of fatigue were described in other neurological diseases such as multiple sclerosis,(18) traumatic brain injury(19) and stroke.(20) We argue that this suggests that even though fatigue is a common symptom in neurological disease, different secondary modifiable conditions can be present in these disorders.(23) In SAH patients there is a high frequency of pituitary dysfunction among which GHD.(12) This might be a possible treatable secondary cause of fatigue in this specific patient population.

We found a decline in the mean level of fatigue in patients without GHD reaching approximately normal levels (mean FSS 4.0) six months after SAH, while mean levels of fatigue were persistently in the pathological range in patients with GHD. Eventually, this did not result in a statistically significant difference in comparison with patients without GHD. The same pattern was visible for subjects with PD where the level of fatigue stayed high as those without PD showed a clear decline in level of fatigue. But in this group the patients without PD did not reach normal levels of fatigue. Fatigue is one of the important clinical features of chronic GHD and of testosterone deficiency in men.(9) The relationship between PD and fatigue after SAH and its effect on the long-term functional outcome has only been evaluated in one other study.(10) Brandt

et al. selected and evaluated ten patients who reported post-SAH fatigue for possible pituitary deficiency, but validated questionnaires were not used, which makes it difficult to compare their results to our findings.

Our results support the notion that the course of fatigue develops differently in patients with GHD than patients without GHD. However, as we found pathological levels of fatigue in a considerable amount of patients without GHD as well, GHD is not an important determinant of persistent pathological level of fatigue after SAH. Therefore we consider fatigue after SAH as a multifactorial problem with GHD or in broader aspect PD as one of the possible determinants that should be taken into account. Pathological levels of fatigue hamper the rehabilitation process(24) and because this process is very important particularly in the first year after SAH, it may be worthwhile to investigate whether PD or GHD is present in SAH survivors. However, the effect of PD and GHD on fatigue is questionable and the effect of growth hormone supplementation or treatment of testosterone deficiency in these groups of subjects has not yet been evaluated. Offering patients with GHD or testosterone deficiency the possibility of hormone supplementation might be seen as a possible treatment option but we do not think that our preliminary results justify this approach or standard hormone supplementation. Obviously, far more patients are needed, preferably in placebo-controlled trials, to evaluate the effect of GHD and hormone supplementation on persisting fatigue after SAH.

To our knowledge we present the largest prospective cohort of SAH survivors in which patients have been analyzed for fatigue in relation to PD. Our study has two main limitations. Firstly, not all participants completed the FSS and, due to the clinical condition, baseline measurements could not be performed in some patients. However, the FSS data of all patients could be analyzed using mixed model analyses. Secondly, we did not measure other factors that may have affected the level of fatigue such as depression or anxiety. Furthermore, we do not have data about the pre-existent fatigue in our subject prior to the SAH.

In conclusion, fatigue is common in SAH patients and those patients with a more severe SAH measured by the WFNS have a tendency for persistence of fatigue in the long term. We think that this is a useful clinical risk factor, which can be used to select patients for counseling and targeted rehabilitation. Patient education and structured rehabilitation have been recommended as treatment for fatigue after SAH.(4) The level of fatigue in patients with GHD remains high over time, but this was not statistically significant different in comparison with patients without GHD. Fatigue itself after SAH could be related to cerebral changes or to a psychological reaction, however PD or GHD could be a factor of chronic fatigue. The clinical value of this finding as a treatable determinant of long-term fatigue after SAH remains questionable.

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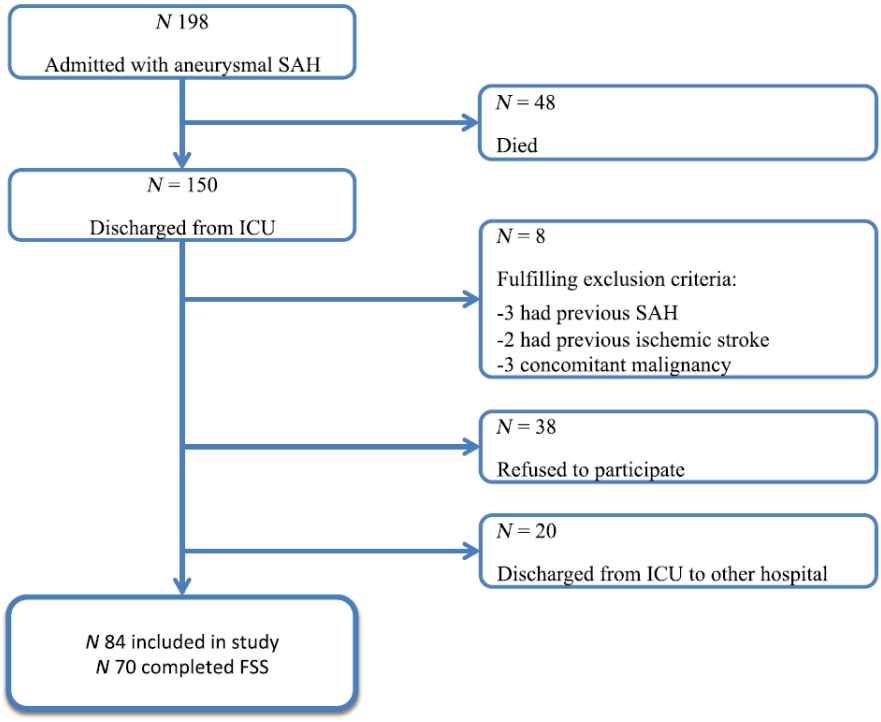
Figure 1. flowchart of patient inclusion.



SAH, subarachnoid hemorrhage; **ICU**, intensive care unit.

Table 1. Patient baseline characteristics

Characteristics N=84	**N (%)***
Mean age (standard deviation)	55.7 (11.9)
Male	28 (33)
History of hypertension	18 (21)
Mean BMI (standard deviation)	25.3 (3.7)
History of smoking	52 (62)
History of hypercholesterolemia	15 (18)
History of DM	4 (5)
GCS on admission	
13-15	66 (79)
9-12	11 (13)
3-8	7 (8)
WFNS on admission	
Grade I	38 (45)
Grade II	25 (30)
Grade III	3 (4)
Grade IV	11 (13)
Grade V	7 (8)
Location of aneurysm	
Anterior circulation	49 (58)
Posterior circulation	35 (42)
Treatment of aneurysm	
Endovascular treatment	66 (79)
Surgical treatment	17 (20)
None	1 (1)
Duration of hospital stay (standard deviation)	18.3 (9.7)

BMI, body mass index; **DM**, diabetes mellitus; **GCS**, Glasgow Coma Scale; **WFNS**, World Federation of Neurological Societies Scale

Table 2. the prevalence of pituitary deficiency and growth hormone deficiency in the Fatigue Severity Scale respondents at different time points

	Baseline	**Six months**	**Fourteen months**
Completed FSS (n)	47	60	52
Mean FSS ≥ 4 (n/ %)	36/ 76%	30/ 50%	31/ 60%
Pituitary deficiency (n/ %)	14/ 30%	17/ 28%	17/ 33%
Growth hormone deficiency (n/ %)	5/ 11%	7/ 12%	8/ 15%

FSS, fatigue severity scale; **n**, number of patients.

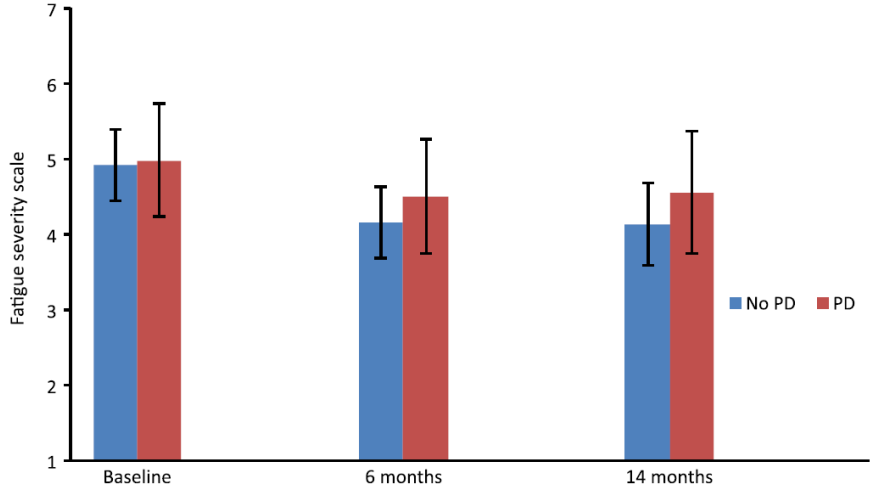


Figure 2. mean score of Fatigue Severity Scale and standard error in patients without pituitary dysfunction (No PD) and patients with pituitary dysfunction (PD), measured at baseline, 6 and 14 months after SAH.

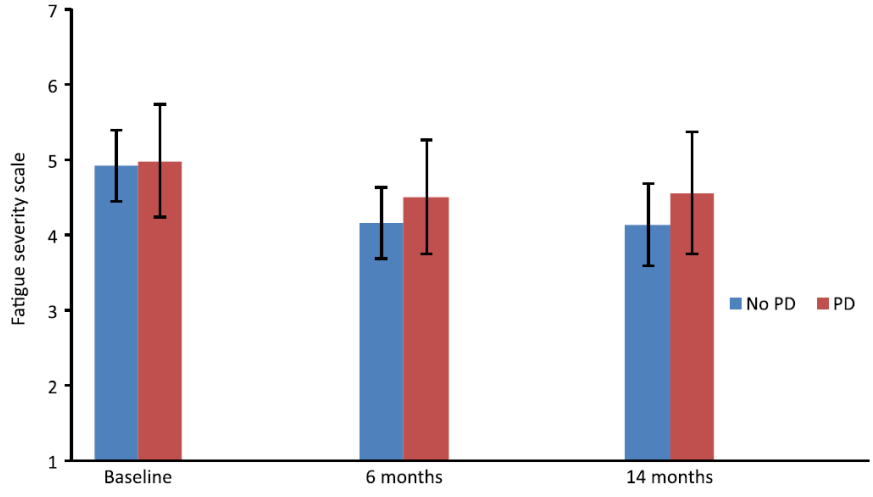


Figure 3. mean score of Fatigue Severity Scale and standard error in patients without growth hormone deficiency (No GHD) and patients with growth hormone deficiency (GHD), measured at baseline, 6 and 14 months after SAH.

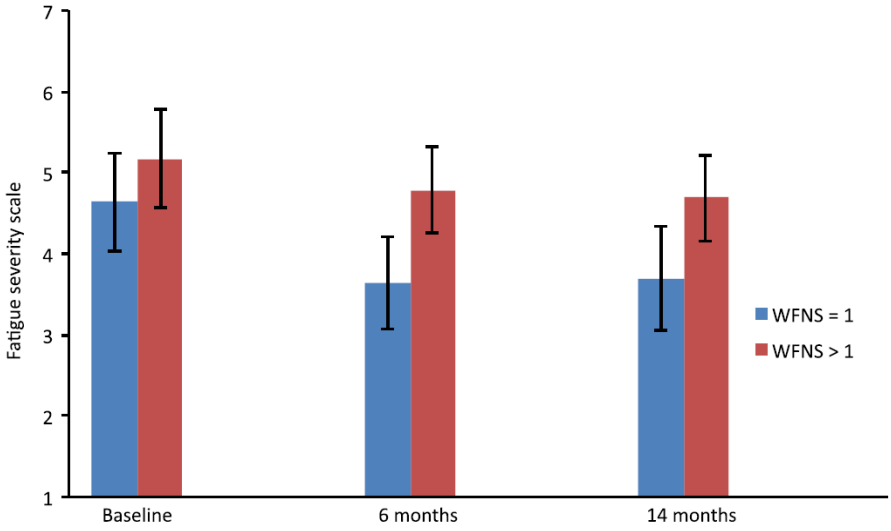


Figure 4. mean score of Fatigue Severity Scale and standard error in patients with World Federation of Neurological Surgeons grading scale 1 (WFNS 1) and patients with WFNS higher than 1, measured at baseline, 6 and 14 months after SAH.


6

Chapter 6

Long-term effect of aneurysmal subarachnoid hemorrhage on physical fitness

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ABSTRACT

Background: physical inactivity, sedentary lifestyles, and low functional outcome are thought to impact the level of physical fitness in patients with aneurysmal subarachnoid hemorrhage (a-SAH). However, changes in fitness over time and associated factors have not been studied in a-SAH. The objective was to evaluate the level of physical fitness in the first year after a-SAH and explore longitudinal relationships with physical activity (PA), sedentary behavior (SB), and functional outcome. Additionally, we have evaluated whether physical fitness could be predicted by disease-related characteristics (ie, severity of a-SAH, location of the aneurysm, treatment procedure, pituitary dysfunction, and complications).

Methods: fifty-two patients performed exercise testing at 6 and 12 months after a-SAH. Cardiopulmonary exercise testing and isokinetic dynamometry were applied to determine the peak oxygen uptake (Vo_{2peak}) and the peak torque of the knee extensors (PT_{ext}) and flexors (PT_{flex}). In addition, PA and SB were evaluated by accelerometer-based activity-monitoring. The functional outcome was assessed by the Functional Independence Measure and Functional Assessment Measure (FIM+FAM). Disease-related characteristics were collected at hospital intake.

Results: at both 6 and 12 months, all fitness parameters were lower compared to predicted values (ranging from 18% to 28%). Positive relationships were found between PA on the one hand and Vo_{2peak} and PT_{flex} on the other, and also between FIM+FAM scores and PT_{ext} and PT_{flex}. Further, patients who underwent surgical clipping had lower Vo_{2peak} and PT_{flex}.

Conclusion: levels of physical fitness remain low over the first year after a-SAH. Patients who were physically more active had higher levels of physical fitness, whereas patients with impaired functional outcome or who were treated with surgical clipping were at risk of low physical fitness. Exercise interventions are warranted and should focus on the promotion of PA and target patients with impaired functional outcome or those who had been treated with surgical clipping.

Introduction

Aneurysmal subarachnoid hemorrhage (a-SAH) is a life-threatening condition and accounts for 3% to 5% of all stroke cases.[1] Depending on its severity, a-SAH is associated with a mortality rate that ranges from 8.3% to 66.7% within the first month.[2] The incidence rate ranges from 4 to 10 per 100.000 persons per year.[3] Most patients regain independence in daily functioning.[4] However, more than two-thirds have an impaired functional outcome such that they experience restrictions in daily life and cannot regain pre-morbid level of functioning.[5, 6] Since the mean age at which a-SAH occurs is reasonably young at 55 years,[3] these restrictions can have a devastating and long-lasting impact on daily living.

Because most patients with a-SAH experience restrictions in daily living, patients may be predisposed to inactive and sedentary lifestyles. This may lead to a negative circle of physical deconditioning. As a consequence, patients may be at risk of low physical fitness.[6] Physical fitness refers to a set of physiological attributes that a person has or achieves, and confers the ability to carry out daily activities without undue fatigue.[7] Cardiorespiratory fitness and knee muscle strength are important aspects of physical fitness and indicative of independent daily living.[8, 9] Previous cross-sectional studies showed impaired cardiorespiratory fitness (62% to 77% of controls) and knee muscle strength (64% to 78% of controls) at 6 months after a-SAH.[10] However, longitudinal studies are warranted to evaluate changes in fitness and related factors over time, which would provide important clinical information and may help to target therapeutic interventions.

Studies in patients with stroke, other than a-SAH, showed long-lasting impairments in cardiorespiratory fitness and knee muscle strength over time, ranging from 26% to 87%, and from 25% to 83% of controls, respectively.[11, 12] These deficits were found in the acute, subacute and chronic phase after stroke (observed up to 8 years after onset).[13] Patients with stroke who were less physically active, more severely disabled, or functionally more compromised are at risk of low physical fitness.[14-16] Since the origin of brain damage differs between patients with ischemic or hemorrhagic stroke and patients with a-SAH (focal vs. diffuse brain damage), it is not clear whether similar factors play a similar role in fitness after a-SAH. In a-SAH, the severity of a-SAH (determined by Glasgow Coma Scale [GCS] score), treatment procedure (surgical clipping vs endovascular coiling), location of aneurysm (anterior vs posterior), and pituitary dysfunction are known predictors of long-term outcome.[3, 4, 17] Therefore, we have investigated whether these disease-related characteristics play a role in physical fitness as well.

The primary goal was to evaluate the level of physical fitness over the first year after a-SAH, and to explore longitudinal relationships with physical activity, sedentary behavior and functional outcome. Secondary, we have evaluated whether physical fitness could be predicted by above-mentioned disease-related characteristics in order to identify patients at risk of low fitness. Repeated measurements of physical fitness, physical activity, sedentary behavior and functional outcome were performed at 6 and

12 months after a-SAH. We hypothesized that physical fitness remains low over the first year, and that inactive and sedentary lifestyles are related to low physical fitness. Further, we hypothesized that patients with lower functional outcome, more severe a-SAH and those who had been treated with surgical clipping are at risk of low physical fitness.

Methods

Participants and Design

This study, entitled HIPS-Rehab, was part of the "Hypopituitarism In Patients after Subarachnoid hemorrhage (HIPS) study."[18] Data collection, clinical definitions of a-SAH and inclusion criteria have been published previously.[10, 18] Personal and disease-related characteristics were collected at hospital intake, and measures of physical fitness, physical activity, sedentary behavior and functional outcome were assessed at 6 and 12 months after onset. This study was approved by the Medical Ethics Committee of the Medical Ethics Committee of the Erasmus MC. All participants provided written informed consent.

Primary Outcome

Physical fitness was assessed by analyzing the cardiorespiratory fitness and isokinetic knee muscle strength. Safety procedures were implemented prior to exercise testing. First, participants fulfilled the Physical Activity Readiness Questionnaire, which is a self-directed assessment to screen for health complications during exercise.[19] Hereafter, participants were screened for medical contraindications to exercise testing by treating neurologist. Exercise testing was not carried out if there was any suspicion of an underlying cardiopulmonary pathology that increases the risk of complications during exercise testing.

The cardiorespiratory fitness was assessed by cardiopulmonary exercise testing (CPET) on an upright cycle ergometer (Jaeger ER800, Jaeger Toennies, Breda, The Netherlands). CPET was preceded by a 4-minute warm-up without resistance after which the resistance increased automatically every 10 sec to ensure that voluntary exhaustion was reached within 10 to 14 minutes (increment for women: 12W/min; men: 16W/min). The test stopped when the participants were not able to maintain target pedal rate (60–70 rpm). CPET could also be terminated because of medical complications, as prescribed by the guidelines of the American College of Sports Medicine (ACSM).[20] During CPET, gas exchanges were analyzed by indirect calorimetry (Oxycon Pro, ViaSys Healthcare, Houten, The Netherlands). Peak oxygen uptake (Vo_{2peak}) was measured at peak physical work rate. Vo_{2peak} was defined as the highest mean peak value during 30 sec of exercise, and expressed in Vo_{2peak} per kilogram body mass ($mL \cdot kg^{-1} \cdot min^{-1}$). In order to determine whether participants reached maximal physical exertion we used the following objective criteria: (I) RER>1.0 or (II) HR_{peak} within 10 bpm of age predicted maximum heart rate (HR_{max}) using the formula: $HR_{max} = 208 - (0.7 \times age)$ Since β-blocker medication can

reduce HRmax by approximately 30%, we adjusted the formula for participants with β-blocker medication: $HR_{max} = 0.7[208 - (0.7 \times age)]$.[10, 21, 22]

Isokinetic knee muscle strength was assessed by dynamometry using the Biodex Dynamometer (Biodex, Shirley, New York, USA). Adjustable seatbelts were used to minimize body movements. The lateral femoral epicondyle was aligned with the rotational axis of the dynamometer. Peak torque (PT) of the knee extensors (PT_{ext}) and flexors (PT_{flex}) were recorded in torque (newton-meters) and corrected for body mass ($N \cdot m \cdot kg^{-1}$). The test protocol involved 5 maximal knee extension and flexion contractions at 60°/s. PT was considered as the maximum torque generated throughout 1 series of repetitions. We calculated the average PT of both limbs because there were no significant differences in PT between the left and right lower limb.

Secondary Outcome

Objective measures of physical activity (PA) and sedentary behavior (SB) were evaluated by accelerometer-based activity monitoring (VitaMove, 2M Engineering, Veldhoven, The Netherlands).[23] The VitaMove consists of 3 individual body fixed recorders (attached to sternum and both legs) (Figure 1). The recorders are wirelessly connected and synchronized every 10 sec. Each recorder has its own accelerometer (Freescale MMA7260Q, Denver, USA). The VitaMove demonstrates validity for quantifying body postures and movements in healthy subjects, and in different patient populations.[23, 24] Activity monitoring measurement started the day after visit, and participants wore the VitaMove on consecutive weekdays, except during swimming, bathing and sleeping. The intended duration of measurement was 3 consecutive days, with a minimum of 1 day.[25] Participants were instructed to continue their ordinary daily activities. The principles of measurement were explained after all measurements were completed in order to avoid measurement bias. Participants kept activity diaries to report reasons of nonwear periods. Accelerometer data were uploaded to a computer for kinematic analyses using VitaScore (VitaScore BV, Gemert, the Netherlands).[23] The following outcome measures were calculated as the mean of available measurement days: duration of PA (including walking, cycling, running, and noncyclic movements; expressed as a percentage of a 24-h period) and duration of SB (including lying and sitting activities; expressed as a percentage of waking hours).

Functional outcome was assessed by treating neurologist using the widely used questionnaire: Functional Independence Measure and Functional Assessment Measure (FIM+FAM).[26] The FIM+FAM consists of 30 items and evaluates functional independence by examining self-care, transfers and mobility, communication, and cognitive and psychosocial daily functioning (FIM+FAM-sores ranging from 1 [total dependence] to 7 [complete independence]. The FIM+FAM showed excellent validity and reliability in patients with stroke.[26]

The following disease-related characteristics were collected at hospital intake: (I) severity of a-SAH by using the Glasgow Coma Scale (GCS) score; (II) location of the aneurysm (anterior vs posterior); (III) treatment procedure (surgical clipping

vs endovascular coiling); (IV) a-SAH complications (rebleeding, delayed cerebral ischemia, hyponatremia, and hydrocephalus); and (V) pituitary dysfunction. Pituitary dysfunction. Methods of endocrine testing and definitions of pituitary dysfunction have been extensively described elsewhere.[18] Endovascular coiling is the preferred treatment modality to close a ruptured aneurysm. Sometimes clipping is the designated treatment modality as coiling cannot be performed (eg, the location of the aneurysm is unreachable via a catheter, the aneurysm is too small, the neck of aneurysm is too wide or the shape of aneurysm is not suitable for coiling).

Data Analysis

All data are expressed as mean (SD) unless otherwise indicated. Differences in clinical characteristics (including sex, age, GCS score, treatment procedure, and location of the aneurysm) between participants in HIPS-Rehab (n = 52) and those who did not participate in the current study (but included in HIPS; n = 32) were verified by independent t-tests for interval variables and by χ^2 tests for categorical variables. Descriptive statistics were used to describe personal and disease-related characteristics. Parametric tests were used because the Shapiro-Wilk test showed that fitness data was normally distributed: Vo_{2peak} (W = 0.979, P = .325), PT_{ext} (W = 0.984, P = .453), and PT_{flex} (W = 0.972, P = .082).

Linear mixed models were created to analyze changes in the estimated mean Vo_{2peak}, PT_{ext}, and PT_{flex} over follow-up time. Visit (6 or 12 months) was entered in the model as a predictor of the dependent outcome. Linear mixed models were created to explore time-dependent relationships between physical fitness (separate models for Vo_{2peak}, PT_{ext}, and PT_{flex}) and 1 of the following factors: PA (%24h), SB (%waking hours) and functional outcome (FIM+FAM scores). The following fixed factors were entered to study whether disease-related characteristics can predict the level of physical fitness: severity of a-SAH (GCS score, range = 1–15), location of the aneurysm (0 = anterior, 1 = posterior), treatment procedure (0 = clipping, 1 = coiling), pituitary dysfunction (0 = no, 1 = yes), and complications (0 = no, 1 = yes).

Prediction equations, established in the general population, were used to predict individual Vo_{2peak}, and served as a comparison.[27] The following equations were used; for men:

$$VO2peak = 23 * height + 11.7 * weight - 31 * age - 32$$
$$VO2peak = 23 * height + 11.7 * weight - 31 * age - 32;$$

and for women:

$$VO2peak = 15.8 * height + 8.99 * weight - 27 * age + 207$$
$$VO2peak = 15.8 * height + 8.99 * weight - 27 * age + 207.$$[27]

To better interpret individual levels of Vo_{2peak}, peak values were additionally classified according to norm data derived from the Cooper Institute.[28] These norm data were gathered in a norm population and classified. Norms were specified by sex and age-category, and Vo_{2peak} values below the 20th percentile of the norm population were considered "very poor." For maximal isokinetic PT_{ext} and PT_{flex} we used the normative data gathered by Sunnerhagen et al (2000).[29]

Linear mixed models are flexible in handling missing values, and these models take into account the covariance between measurements within patients. Each model was adjusted for sex (0 = women, 1 = men) and age. Statistically, sex and age were not always significant confounders, but were kept in each model because these factors are considered of fundamental importance in research on physical fitness,[30] leading to the following linear mixed model equation:

$$Y(\text{Fitness}) = \beta 0 + \beta 1 \cdot \text{Visit} + \beta 2 \cdot \text{Age} + \beta 3 \cdot \text{Sex} + \beta 4 \cdot \text{Predictor} + \varepsilon$$

We reported estimated beta-coefficients, effect sizes (Cohen *d*), 95% confidence intervals and *P* values. The significance level was set at $P < .05$. Bonferroni correction was applied to adjust for type I error for multiple testing (SPSS Inc, Chicago, IL, USA).

Results

In total, 241 patients were admitted to the Intensive Care Unit with a diagnosis of a-SAH;[18] of the 84 eligible patients 52 participated in the present study. Participants in HIPS-Rehab (n = 52) did not differ from those who did not participate in the current study (but included in HIPS; n = 32) with respect to: age ($T(84) = -0.005$, $P = .996$), sex ($\chi^2(1) = 0.066$, $P = .291$), GCS score ($T(84) = 1.505$, $P = .136$), location of the aneurysm ($\chi^2(1) = 0.092$, $P = .469$) and treatment procedure ($\chi^2(1) = 0.086$, $P = .489$). Fifty-two participants were assessed at 6 months, and 42 were assessed at 12 months after onset (Tab. 1). Patients with complete follow-up (n = 42) did not differ from those lost to follow-up (n = 10) with respect to: age ($T(52) = 1.269$, $P = .210$), sex ($\chi^2(1) = 0.495$, $P = .264$), GCS score ($T(52) = -1.282$, $P = .230$), location of the aneurysm ($\chi^2(1) = 0.001$, $P = .634$), treatment procedure ($\chi^2(1) = 0.581$, $P = .353$), complications ($\chi^2(1) = 0.288$, $P = .464$). Since we used linear mixed model analyses data of most patients could be included in the final analyses because this method allows patients in the analyses for who some of the data is missing (Figure 2 presents a detailed flow diagram).

Data were not available for all participants. CPET data of 43 patients were included in the final analyses (83% of the sample). In total, 6 patients were not able to perform CPET due to contra-indications (n = 3), logistical reasons (n = 2) and because of an additional injury (n = 1). Furthermore, CPET data of 3 patients did not meet the objective criteria for maximal physical exertion and were excluded. In total, 9 patients with successful CPET were on beta-blocker medication. Isokinetic dynamometry data of 48 patients were included (92% of the sample); 3 were not able to perform isokinetic dynamometry because of medical reasons and 1 because of logistical reasons. Activity

monitoring data of 44 patients were included (85% of the sample); measurements in 4 patients were lost due to technical failure, 3 because of logistical reasons and 1 because of refusal.

Physical Fitness

The estimated mean Vo_{2peak} in patients increased between 6 and 12 months by +6.2% (β = 1.417 mL·kg^{-1}·min^{-1}, P = .027), while there was a nonsignificant trend for an increase of +5.1% in PT_{ext} (β = 0.071 N·m·kg–1, P = .061) (Tab. 2). The estimated mean PT_{flex} did not change over time (β = 0.026 N·m·kg–1, P = .281). Although patients managed to exercise towards acceptable cardiorespiratory limits at both follow-up times, the estimated mean peak respiratory exchange ratio at 6 months was lower compared to 12 months, 1.13 (SE 0.01) vs. 1.19 (SE 0.02), respectively (P < .001). The estimated mean Vo^{2peak} was 28% higher in men than in women (β = 6.606, P = .001), Vo_{2peak} decreased 8% per 10 years of age (β = –1.601, P = .021). Further, Vo_{2peak} in patients who were on beta-blocker medication did not differ from those who were not on beta-blockers (β = –2.333, P = .214).

Figure 3 shows a graphic presentation of the differences in the estimated Vo_{2peak}, PT_{ext} and PT_{flex} between patients and predictive values. The estimated mean Vo_{2peak} at 6 and 12 months were significantly lower than the predicted values calculated from the formulas established by Fairbarn et al (1994)[27]: 26% lower at 6 (β = –7.865 mL·kg^{-1}·min^{-1}, P <.001) and 21% lower at 12 months (β = –6.537 mL·kg^{-1}·min^{-1}, P < .001).[27] According to the classifications made by the Cooper Institute, at 6 and 12 months, the Vo_{2peak} was considered very poor in respectively 43% and 39%.[28] Analyzing individual change (criterion: ± 2.0 mL·kg^{-1}·min^{-1}),[31] showed that the Vo_{2peak} improved in 30%, remained stable in 48% and deteriorated in 22% of the patients. At both 6 and 12 months, the knee muscle strength was significantly lower than predicted values.[29] At 6 months, PT_{ext} was 22% lower (β = –0.344 N·m·kg^{-1}, P < .001) and PT_{flex} 28% lower than predicted values (β = –0.282 N·m·kg^{-1}, P < .001); at 12 months, PT_{ext} was 18% lower (β = –0.216 N·m·kg^{-1}, P < .001) and PT_{flex} 22% lower than predicted values (β = –0.186 N·m·kg^{-1}, P < .001).[29]

Determinants of Physical Fitness

Table 3 presents the results of the linear mixed models, evaluating the determinants of physical fitness. Total PA (%24h) was positively associated with Vo_{2peak} (β = 0.638 mL·kg^{-1}·min^{-1}, P = .006) and PT_{flex} (β = 0.018 N·m·kg^{-1}, P = .037), indicating that patients who were physically more active had higher cardiorespiratory fitness and knee flexion strength. The functional outcome (FIM+FAM score) was significantly related to PT_{ext} (β = 0.125 N·m·kg^{-1}, P = .004) and PT_{flex} (β = 0.057 N·m·kg^{-1}, P = .042), indicating that patients with lower functional outcome had lower knee extension and flexion strength. There was no evidence for a relationship between SB and physical fitness.

Further, patients who had been treated with surgical clipping had 22% lower Vo_{2peak} (β = −4.946 mL·kg^{-1}·min^{-1}, *P* = .008) and 29% lower PT_{ext} (β = −0.176 N·m·kg^{-1}, *P* = .029) compared to those who underwent endovascular coiling. Figure 4 presents the change in physical fitness over the first year, specified by treatment procedure (surgical clipping vs. endovascular coiling). Other baseline characteristics of interest such as severity of a-SAH (GCS score), location of the aneurysm and pituitary dysfunction were not associated with physical fitness.

The estimated beta-coefficients are presented in Table 3 and reflect the change in fitness that is associated with a 1-unit change in the predictor. In this example we lighten the finding that patients who were physically more active had higher Vo_{2peak} (β = 0.638 mL·kg^{-1}·min^{-1}); patients with +1% higher PA have a higher Vo_{2peak} of +0.638 mL·kg^{-1}·min^{-1}. This finding indicates that 3.1% higher physical activity levels (45 min/24h) are associated with a +2.0 ml/kg/min higher Vo_{2peak}.

Discussion

This 1-year follow-up study showed that patients with a-SAH have low physical fitness over the first year.[27, 28] More than one-third of the patients had Vo_{2peak} values that were considered very poor at both 6 and 12 months after onset. Patients who were physically more active had higher peak oxygen uptake and knee flexion strength, and patients with lower functional outcome had lower knee extension and flexion strength. Further, patients who had been treated with surgical clipping are at risk of low physical fitness. Our findings indicate that exercise interventions are warranted. Such intervention should involve both cardiorespiratory endurance and muscle strengthening components and should consider the promotion of PA. Further, these interventions should target patients with impaired functional outcome or those who had been treated with surgical clipping.

The applied treatment procedure to close the aneurysm was found to be a predictor of physical fitness. The Vo_{2peak} of patients who had been treated with surgical clipping was 22% lower compared to those who underwent endovascular coiling; this was 29% for knee flexor strength. Our findings indicate that endovascular coiling favors surgical clipping which is in line with a recent meta-analysis that showed that endovascular coiling yields optimal clinical outcome compared to surgical clipping.[32] Professionals should be aware of the fact that patients who had been treated with surgical clipping are at risk of poor health outcome. This finding may help to target future interventions in patients with a-SAH.

The observed deficits in physical fitness (18% to 28% lower than reference) were smaller compared to patients with other types of stroke; where fitness parameters were 13% to 75% lower than healthy controls.[11, 12] This may be explained by the fact that patients with ischemic or hemorrhagic stroke are often more disabled due to focal brain damage and neuro-motor lesions, and therefore, less likely to maintain active lifestyles. In line with our findings, studies in stroke showed negative relationships between functional

outcome and knee muscle strength.[33] Further, the reported deficits in our group are comparable to patients with transient ischemic attack (TIA) and patients with minor ischemic stroke (21% to 35% lower than controls).[14, 34]

Physical activity has been related to improved physical fitness across different patient groups (eg, coronary heart disease, diabetes mellitus, obesity, and stroke).[9, 15] In our sample we also found that patients who were physically more active had higher Vo_{2peak}. The observed relationships between activity and fitness in a-SAH are in line with research in patients with stroke, where higher levels of physical activity were positively associated with higher levels of fitness.[35] The estimated beta-coefficient for PA showed that patients with higher PA (45 mins per 24h) have a 2.0 $mL \cdot kg^{-1} \cdot min^{-1}$ higher Vo_{2peak} (= reflects criterion improvement in stroke).[31] Future intervention studies are warranted to investigate whether increased levels of PA leads to improved Vo_{2peak} in patients with a-SAH. Since PA in our study is based on total PA time, regardless of intensity of activities, this means that walking or household activities are already associated with higher Vo_{2peak}. However, from research in sports and exercise we know that the intensity of PA plays a decisive role in fitness.[7, 15] Future studies are warranted to investigate optimal treatment paradigms to improve fitness in patients with a-SAH.

SB and PA are 2 different constructs, in that SB is more than merely a lack of PA (too little exercise), it is rather a behavioral entity that may have distinct physiological effects independent of the amount of PA.[36] Physically active individuals who satisfy recommendations for optimal PA may still be sedentary for their remaining waking hours. In our study we did not observe any relationship between SB and physical fitness. Although associations between physical inactivity and low physical fitness are well-established,[9] future studies are warranted to better understand relationships between SB and physical fitness.

The longitudinal models were corrected for sex and age. According to the estimated beta-coefficients, female sex and higher age were negatively associated with physical fitness. However, the finding that Vo_{2peak} in women was approximately 28% lower than in men, and the fact that Vo_{2peak} decreased 8% per 10-years of age are similar to findings in the general population.[37, 38]

Studies in patients with non a-SAH stroke, showed that exercise training can improve the cardiorespiratory fitness by 9% to 23%.[39] Furthermore, exercise training can reduce depressive symptoms, prevent complications associated with physical inactivity, and decrease the likelihood of recurrent stroke.[15, 40] There may be important health benefits from exercise training for patients with a-SAH as well. However, exercise interventions are lacking in a-SAH. Future intervention studies are warranted to investigate the beneficial effects of exercise training in patients with a-SAH.

Previous studies have already shown that cognitive impairments and psychological factors, such as mood and anxiety, lowers the functional outcome after a-SAH.[4] In this study we provide evidence for an association between physical fitness and functional outcome. Our results revealed that FIM+FAM scores were associated to knee extension

and flexion strength, indicating that patients with lower muscle strength had lower functional outcome. From ageing studies we know that improved knee muscle strength contribute to functional outcome and independent daily living.[41] It could be argued that improved knee muscle strength may also improve functional outcome in a-SAH. However, future intervention studies are warranted to investigate whether strengthening exercise improves functional outcome in a-SAH.

Interventions in stroke-rehabilitation mainly focus on the performance of daily activities.[15] As a result, there are is a lack of interventions targeting fitness after stroke.[40] Our findings indicate that exercise interventions in a-SAH should involve both cardiorespiratory endurance and strengthening exercise components. One could speculate that Interval training may be advantageous in a-SAH, to challenge the cardiorespiratory system without exhausting the muscular system.[15] Further, since we found a positive relationship between PA and physical fitness, future exercise programs may also consider the promotion of daily PA in patients with a-SAH.

Limitations

Some critical reflections are warranted. First, not all measurements were available for all patients which may have led to selection bias. However, the data of most patients could be included in the final analyses by estimating the mean outcome using linear mixed model analyses. This statistical method takes into account the covariance between measurements within patients. In total, 3 patients had absolute contra-indications to exercise testing and did not perform fitness measurements. Since these patients are more likely to abstain from exercise, we may have underestimated fitness deficits in patients with a-SAH. Second, we could not confirm causality between parameters. However, the longitudinal relationships provide important clinical information about co-existence of problems and may help to direct therapeutic options in a-SAH. Third, interaction terms could not be studied because of insufficient statistical power (sample size of n = 52). However, since fitness parameters did not, or only slightly change over follow-up time, we do not expect to find interaction effects in our data. Ideally, a CPET practice trial should have been implemented as practice effects of CPET may lead to improvements in CPET performance.[42] Therefore, the observed improvement in Vo_{2peak} may be an overestimation of the actual improvement. However, implementing an additional practice trial was not feasible within our study. Activity monitoring measurements covered 3 consecutive weekdays and started the day after visit. It remains questionable whether short measurement periods are representative of routine physical activity. However, 3-day measurement-schedules have been frequently used to objectively determine physical activity in daily life.[24] Finally, selection bias may have occurred towards patients who are interested in sports and exercise which may have led to an underestimation of physical fitness deficits. However, participants did not differ from those who did not participated in HIPS-Rehab but were included in HIPS.

Conclusion

In summary, physical fitness remained low over the first year after a-SAH. More than one-third of the patients had very poor levels of Vo_{2peak} at 6 and 12 months after onset.[28] Our findings revealed that patients who were physically more active had higher peak oxygen uptake and knee flexion strength, whereas patients with lower functional outcome had lower knee extension and flexion strength. Further, patients who had been treated with surgical clipping are at risk of low physical fitness. Exercise interventions are warranted and may consider the promotion of daily PA and should target patients with lower functional outcome or those who had been treated with surgical clipping. Future research is warranted to investigate whether rehabilitation services can adapt their programs for patients with a-SAH in order to meet the needs of these patients.

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Table 1. Characteristics of 52 Participants With Aneurysmal Subarachnoid Hemorrhage[a]

Characteristic	Value for Participants[b]
Age, y, mean (SD)	56.1 (13.5)
Sex, men	16 (31)
GCS score, mean (SD)	13.5 (2.1)
Location of aneurysm	
Anterior	31 (60)
Posterior	21 (40)
Treatment procedure	
Endovascular coiling	47 (90)
Surgical clipping	11 (21)
Secondary complications	
Rebleeding	0
Delayed cerebral ischemia	7 (13)
Hyponatremia	6 (12)
Hydrocephalus	13 (25)
Pituitary dysfunction	24 (46)

[a]GCS = Glasgow Coma Scale.

[b]Data are presented as number (percentage) of participants unless otherwise indicated.

Table 2. Estimated Values for Vo_{2peak}, Knee Extensor and Flexor Strength, and Daily Physical Activity and Sedentary Behavior and Significance Level of Change Over Time[a]

Physical Fitness	Mean (SE) at:		Change From t1 to t2[b]	95% CI for Change	Cohen dc	P
	6 mo (t1)	12 mo (t2)				
Cardiorespiratory fitness						
Vo_{2peak}, $mL \cdot kg^{-1} \cdot min^{-1}$	22.79 (0.94)	24.20 (0.91)	+1.417	0.170 to 2.664	0.257	.027[d]
HR_{peak}, % of predicted HR_{max}	88.59 (2.37)	90.42 (2.32)	+1.824	−1.398 to 5.054	0.132	.255
RER_{peak}, VCo_2/Vo_2	1.13 (0.01)	1.19 (0.02)	+0.058	0.034 to 0.081	0.653	<.001[d]
Knee muscle strength						
PT^{ext}, $N \cdot m \cdot kg^{-1}$	1.38 (0.06)	1.45 (0.06)	+0.071	−0.004 to 0.146	0.185	.061[c]
PT^{flex}, $N \cdot m \cdot kg^{-1}$	0.61 (0.04)	0.64 (0.04)	+0.026	−0.022 to 0.073	0.119	.281

[a]All determinants were entered separately with adjustment for sex and age. HR_{max} = maximum predicted heart rate HR_{peak} = peak heart rate; PT_{ext} = peak torque of the knee extensors; PT_{flex} = peak torque of the knee flexors; RER_{peak} = peak respiratory exchange ratio; VCo_{2peak} = Vo_{2peak} = peak oxygen uptake.

[b]Estimated mean change over follow-up time.

[c]Cohen $d = \frac{\mu 2 - \mu 1}{\Sigma \sigma} \frac{\mu 2 - \mu 1}{\Sigma \sigma}$.

[d]Significant difference ($P < .05$).

[e]Nonsignificant trend for a difference ($P < 0.10$).

Table 3. Determinants of Cardiorespiratory Fitness (VO_{2peak}) and knee muscle strength (PT_{ext} and PT_{flex})[a]

Linear Mixed Model	Vo_{2peak} in mL·kg^{-1}·min^{-1} (n = 43)			PT_{ext} in N·m·kg^{-1} (n = 48)			PT_{flex} in N·m·kg^{-1} (n = 48)		
	β[b]	95% CI for β	P	β[b]	95% CI for β	P	β[b]	95% CI for β	P
Time	+1.417	0.170 to 2.664	.027	+0.071	−0.004 to 0.146	.061	+0.026	−0.022 to 0.073	.281
Sex	+6.606	3.062 to 10.150	.001c	+0.340	0.120 to 0.561	.003[c]	+0.214	0.075 to 0.353	.003c
Age	−0.160	−0.295 to −0.025	.021	−0.012	−0.020 to −0.003	.010	−0.009	−0.015 to −0.004	.002[c]
Physical behavior and functioning									
Physical activity	+0.638	0.193 to 1.082	.006	+0.023	−0.009 to 0.056	.147	+0.018	0.001 to 0.036	.037
Sedentary behavior	−0.030	−0.201 to 0.142	.726	−0.004	−0.013 to 0.006	.459	−0.002	−0.004 to 0.008	.556
Functional outcome[d]	+0.469	−1.031 to 1.969	.531	+0.125	0.041 to 0.209	.004[c]	+0.057	0.002 to 0.112	.042
Baseline characteristics									
GCS score	+0.103	−0.708 to 0.914	.799	+0.037	−0.010 to 0.084	.116	+0.022	−0.008 to 0.053	.146
Location of aneurysm	+1.191	−2.059 to 4.441	.463	+0.105	−0.101 to 0.310	.311	+0.048	−0.082 to 0.179	.459
Treatment	−4.946	−8.528 to −1.365	.008	−0.135	−0.396 to −0.126	.302	−0.176	−0.333 to −0.018	.029
Pituitary dysfunction	−1.312	−4.531 to 1.908	.415	−0.009	−0.216 to 0.197	.928	−0.066	−0.195 to 0.063	.306
Complications	−0.524	−3.809 to 2.762	.749	−0.110	−0.324 to 0.104	.305	−0.071	−0.205 to 0.064	.295

[a]Each of the following determinants was included in a separate linear mixed model with adjustment for sex (0 = female; 1 = male) and age (y): time (0 = 6 mo; 1 = 12 mo), physical activity (% of 24 h), sedentary behavior (% of waking h) Functional Independence Measure and Functional Assessment Measure (range = 1–7), Glasgow Coma Scale (GCS) score (range = 1–15), location of aneurysm (0 = anterior; 1 = posterior), treatment (0 = coiling; 1 = clipping), pituitary dysfunction (0 = no; 1 = yes), and secondary complications (0 = no; 1 = yes). PT_{ext} = peak torque of the knee extensors; PT_{flex} = peak torque of the knee flexors; Vo_{2peak} = peak oxygen uptake (mL·kg^{-1}·min^{-1}).

[b]Estimated β coefficient.

[c]Significant predictor of physical fitness after Bonferroni correction: $P = .05/10 = .005$.

[d]Functional outcome was determined with the Functional Independence Measure and Functional Assessment Measure questionnaires.

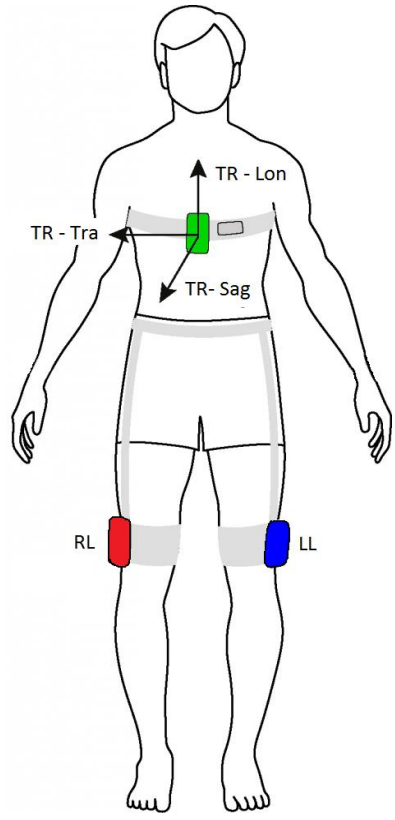

Figure 1. Placement of the VitaMove activity monitor. Abbreviations: TR= Trunk sensor; RL= Right leg sensor; LL= Left leg sensor; Lon= longitudinal axis; Sag= sagittal axis; Tra= transversal axis.

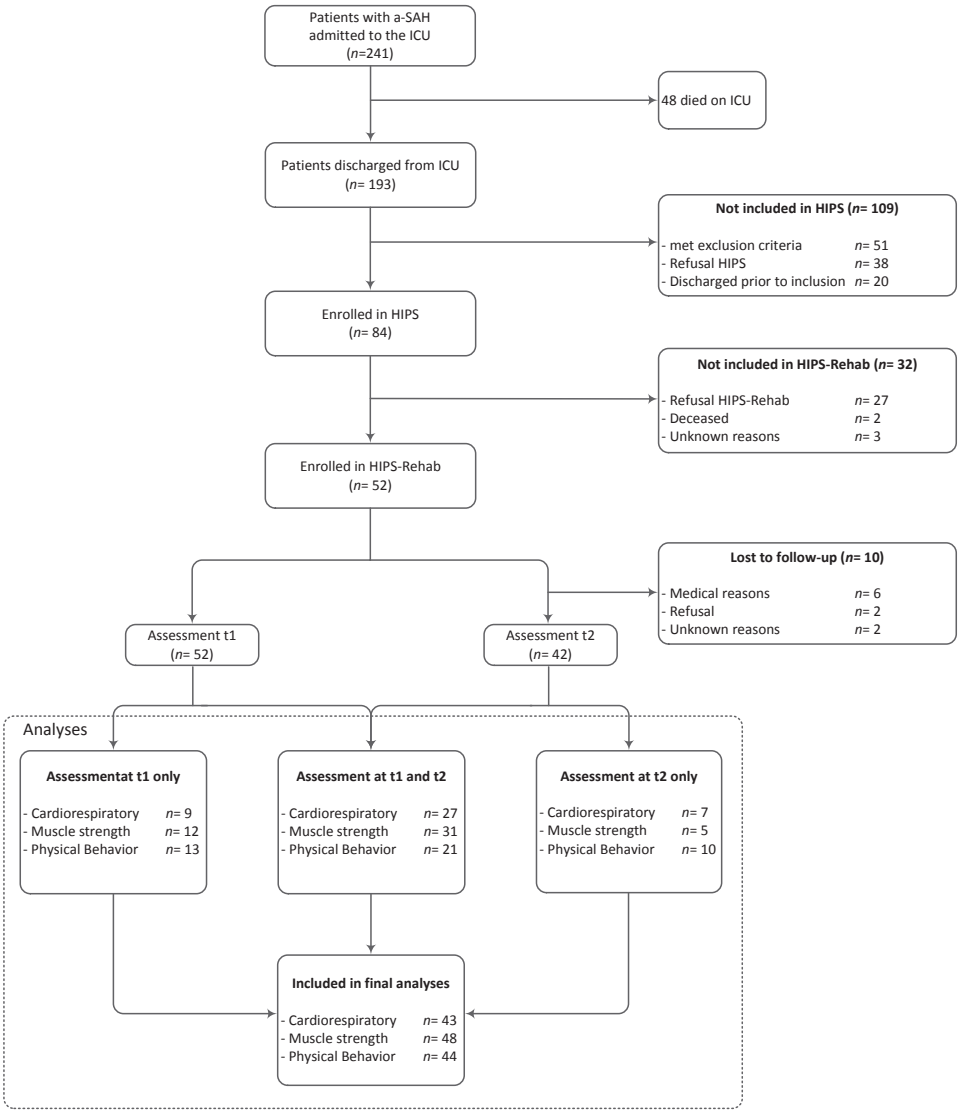

Figure 2. Flow diagram.

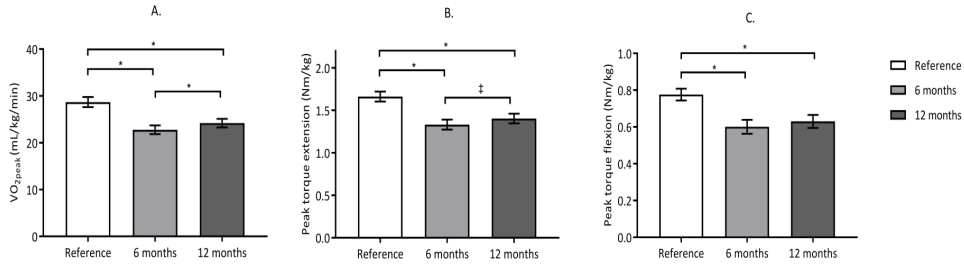

Figure 3. Graphic presentation of the estimated mean (SE) for Vo_{2peak} (A), peak torque knee extension (B), and peak torque knee flexion (C) at 6 and 12 months after aneurysmal subarachnoid hemorrhage (a-SAH) compared to reference values. Reference values for Vo_{2peak} were calculated from Fairbarin et al,[27] and reference values for PT_{ext} and PT_{flex} were calculated from Sunnerhagen et al.[29] *Significant difference ($p < .05$)

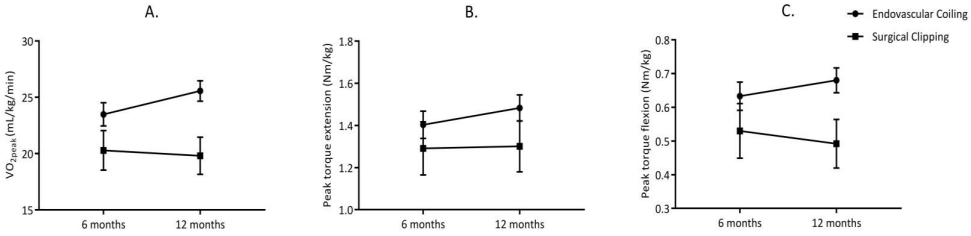

Figure 4. Graphic presentation of the estimated mean (SE) for Vo_{2peak} (A), peak torque extension (B), and peak torque flexion (C) at 6 and 12 months for patients who underwent surgical clipping or endovascular coiling. Surgical clipping was negatively associated with Vo_{2peak} ($P = .008$) (A) and peak torque flexion ($P = .029$) (C).

Chapter 7

General discussion

This thesis concerns hypopituitarism after SAH with a focus on screening, incidence and predictors and its relation with the long-term outcome and more specifically with fatigue.

In this chapter the most important findings of this thesis, it's strengths and limitations and clinical implications are discussed. Finally, recommendations for future studies are presented.

Main findings in context

Review of the literature

A systematic review (chapter 2) showed a large variability with incidences between 0 and 55%. There was a significant variability in quality and methodology of the published studies. The most prominent methodological shortcomings were the incomplete reports of patient selection [1-6], obvious selection bias[3-7] and inadequate laboratory testing [3, 4, 6, 8-10]. Some studies did not use dynamic tests to determine growth hormone or corticotrophin deficiency[4, 5, 7, 9]. In some reports, description of the statistical analysis and results were incomplete[8] or even absent[3]. Remarkably, we found a difference between the results of the older studies and the more recent studies. Older studies[7, 11, 12] reported a higher occurrence of hypopituitarism than more recent studies[13, 14]. This can be a consequence of only using basal hormone tests in some of these studies instead of using adequate dynamic tests to determine hypopituitarism.

After review of the literature, we were not able to find consistent evidence for significant predictors of hypopituitarism after SAH. Hydrocephalus, vasospasm and female sex were noted as possible determinants in some studies but other investigators could not confirm these findings.

In summary, although some evidence supports the hypothesis that hypopituitarism is a complication of SAH, its incidence differed strongly between studies and strong predictors could not be found. Further, predictors for hypopituitarism after SAH could not be extracted, neither a reliable method for diagnosing hypopituitarism after SAH and the relation between hypopituitarism and long-term outcome is not clear.

Early screening for hypopituitarism after SAH

Chapter 3 is a clinical study on a reliable and safe method to screen patients for hypopituitarism as early as possible after SAH. The gold standard for the diagnosis of GHD is the insulin tolerance test, which if contraindicated as in patients with ischemic heart disease and seizures, is regularly replaced by the GHRH arginine test, which is well-validated in adults [15]. Both tests have side effects such as vasodilatation and paresthesias[16], and therefore their use cannot be recommended in the early phase after SAH because these side effects might be confused with symptoms of delayed cerebral ischemia which also can present with paresthesia as a symptom. A ghrelin test is not limited by side effects and it has the advantage that it stimulates both GH and ACTH

release. By its binding to the GH receptor type 1a, ghrelin has a strong GH releasing activity, and can be used as diagnostic test. Ghrelin also results in other hypothalamic activities leading to stimulation of prolactin (PRL) and ACTH secretion[17]. The ghrelin test had not been used in SAH patients before.

The ghrelin test has been shown by others to be a reliable diagnostic test for GHD in adults with clear cut off limits in lean and overweight patients[18]. Side effects such as facial flushing have been observed by other investigators in a smaller group of patients comparing the ghrelin test compared with the GHRH arginine test. Besides that, other side effects of ghrelin test have not been described so far, except transient hyperhidrosis with high doses of ghrelin [19, 20].

We found that a cut-off limit of a GH peak of 15 μg/L corresponded with a sensitivity of 100% and a false positive rate of 40% after Ghrelin test in GHD subjects. Except one patient with flushing no adverse events or idiosyncratic reactions were observed in subjects undergoing a ghrelin test. Our results show that the ghrelin test is a safe and valid alternative test shortly after SAH. This allows early performance of routine screening for hypopituitarism by using a combination of basal hormonal tests and the ghrelin test as a safe dynamic test for GHD or ACTH deficiency.

Occurrence of hypopituitarism after SAH

Chapter 4 explores the incidence of hypopituitarism after SAH and the issue whether hypopituitarism after SAH is a temporary reactive phenomenon or a long-lasting complication of SAH.

More than one third of survivors of aneurysmal SAH were deficient in one or more pituitary axes at baseline. Gonadotropin and growth hormone were the most often affected pituitary hormones. Over time, there was a decline in rate of pituitary dysfunction (39% early after SAH, 26% at 6 months and 7% at 14 months after SAH).

The recovery of pituitary function over time has been described in other studies,[13, 21]. This decline over time may be caused by the ability of the pituitary gland to regenerate after injury,[22] which might explain the recovery of pituitary function in our patients. Nevertheless, the high number of patients with hypopituitarism early after SAH can still be of significant importance. SAH survivors are often fatigued and some are troubled by cognitive or physical dysfunction[23]. As pituitary dysfunction can lead to symptoms such as fatigue and lower physical fitness which can lead to less ability to take part in rehabilitation and by this leading to a longer or maybe even less well recovery[24]. For this reason, it is important to know if hypopituitarism is associated with these complaints in SAH survivors. This matter will be covered in chapter 5 and 6 of this thesis.

Clinical predictors of hypopituitarism

In our cohort described in chapter 4, hydrocephalus was associated with PD six months after SAH and male sex was associated with persistent GHD.

Cerebral vasospasm and hydrocephalus have previously been identified as risk factors for pituitary dysfunction[7]. Other studies also describe other clinical predictors, such as female sex and the presence of corticotrophin deficiency[6], younger age, pituitary dysfunction[9] while others found higher age to be associated with growth hormone deficiency after SAH[21]. These associations were not confirmed by other studies [2, 4, 13, 18, 25]. This shows that there is a need for more confirmation of the clinical predictors before the pituitary testing can be solely preformed in a subgroup of SAH survivors which would reduce the burden and the cost of screening for hypopituitarism. Even though there is also a decline in frequency of hypopituitarism overtime, we still have to be alert of clinical symptoms of SAH survivors which resemble symptoms of hypopituitarism and preform endocrine testing in these patients to exclude a possible hypopituitarism as a small part of patients do have persistent hypopituitarism. Therefor consider early neuro-endocrine evaluation of SAH patients but only in patients predicted to be at risk by having clinical predictors and symptoms as mentioned above. As it can have an effect in the early phase after SAH as ACTH deficiency can occur and be life threatening in this phase and also later on in the course as rehabilitation process can be hampered by pituitary dysfunction (PD).

Fatigue after SAH

76% of the cohort of SAH patients described in chapter 5 suffered from a pathological level of fatigue defined as a mean score of 4 or higher in the fatigue severity scale (FSS) [26] . Although this number diminished over time, still 60% of the patients had pathological levels of fatigue after 14 months. This finding is in line with studies which have established the existence of high proportion of patients with fatigue after SAH [27, 28]. Because fatigue is a frequent complaint of SAH survivors [3] and hypopituitarism specifically GHD can result in fatigue[24], we studied the possible association between fatigue and hypopituitarism after SAH.

Fatigue in relation to pituitary function

No statistically significant differences in occurrence of fatigue over time in patients with or without PD or GHD were found in chapter 5. However a trend was observed as the mean level of fatigue in patients without GHD declines and reaches approximately normal levels (mean FSS 4.0) six months after SAH, while mean levels of fatigue persisted in the pathological range in patients with GHD. We also detected a statically significant decline of the fatigue levels measured by FSS in patients without PD over time while this decline was not seen in the patients with PD.

One earlier study has addressed the possible association between PD and fatigue after SAH. [3] In this study a selected group of patients was evaluated for post stroke fatigue and its possible association with pituitary deficiency. It was concluded that hypopituitarism might contribute to fatigue after SAH but due to a small number of patients and selection bias, no clear conclusions nor recommendations can be made.

Our results suggest that the course of fatigue develops differently in patients with PD or GHD than patients without PD or without GHD. However, as we found pathological levels of fatigue in a considerable number of patients without PD or GHD as well, PD or GHD are not the only, or most important determinant of persistent pathological level of fatigue after SAH. Therefore, we consider fatigue after SAH as a multifactorial problem with GHD or in broader aspect PD as one of the possible determinants that should be taken into account.

Physical fitness after SAH

Hypopituitarism can result in various clinical symptoms. One of the common clinical symptoms of growth hormone deficiency is decreased muscle mass and strength. Furthermore chronic corticotropin deficiency and thyrotropin deficiency can result in fatigue and tiredness [24]. Low physical fitness is one of the factors which might influence the functional outcome in SAH survivors as lower cardiorespiratory fitness is common in SAH survivors [29]. Further evidence for the long-term effect of hypopituitarism was sought by analysis of impaired physical fitness which could influence the functional outcome.

Our results confirm the previous finding that SAH survivors have low physical fitness over the first year without improvement during that time period [30,31]. We also found that SAH survivors who were physically more active had better physical fitness after one year. We did not find an association between PD and lower physical fitness.

Physical fitness can be seen as physiological conditions that a person has or achieves, and confers the ability to carry out daily activities without undue fatigue [32]. Understanding the mechanisms how physical fitness is affected by SAH can give us information which might be used in personalizing treatment for SAH survivors. Previous studies have shown that passive coping style among others, has a negative effect on the resumption of work and daily activities in SAH survivors [33, 34]. Furthermore, earlier studies have assumed a relation between fitness, fatigue and activity in which there is an interaction between these factors[35]. This may explain why physically active patients have a better physical fitness in comparison to patients with a lower physical fitness as one factor does enforce the other. Our study is the first to investigate an association between physical fitness and hypopituitarism. Earlier studies did find inconsistent evidence on the effect of hypopituitarism on Health Related Quality of life (HR-QoL) [10, 36, 37].

We found lower physical fitness in patients who have had surgical clipping compared with patients who had coiling which is in accordance with other studies. This might be explained by the longer hospitalization and a greater chance of dependency of the patients in the first year after SAH[38]. A recently published meta-analysis found physical disability to be the most important predictor of poor quality of HR-QoL after SAH[39]. On the other hand a review by Passier et al found higher age, female sex, clinical condition on admission, fatigue, disturbed mood, physical disability, cognitive complaints, neuroticism and passive coping as determinants of impaired quality of life after SAH and not only physical disability[40]. These contradictive findings make it

difficult to use these different predictors among which physical fitness in every day practice for selection of patients who are prone to lower HR-QoL for further intensive therapy or evaluation.

Methodological considerations

Strengths and limitations.

Our study is the largest prospective cohort of SAH survivors in whom the occurrence of hypopituitarism has been studied. We describe a reliable and valid tool that can be used to screen for hypopituitarism after SAH. This tool gave us the opportunity to safely screen for hypopituitarism in the first few weeks after SAH. We were able to establish the course of hypopituitarism over time and to look for clinical determinants for hypopituitarism. We were able to study the relationship between fatigue and hypopituitarism and between physical fitness and hypopituitarism after SAH.

We have to recognize some general limitations of the studies in this thesis. Even though our study is the largest prospective observational study, the number of participants in our study does restrict us in the data analysis where the number of variables that can be used for the interaction between variables is limited. Furthermore, our results should be interpreted with caution as finding an association in observational studies is not equal to a causal relation between the variables[41].

In chapter 3 the time-interval between different GH stimulation tests could have influenced the frequency of GHD found with the ghrelin test and GHRH- arginine test. Ghrelin test was performed in the first 3 months after SAH while GHRH-arginine test was carried out at least six months after SAH. Hypopituitarism early after SAH has been described to resolve[2, 42]. This might have caused an underestimation of the number of patients with GHD in the early phase after SAH as the confirmatory test was performed at least 3 months later in the course. Ideally, multiple simultaneous GHD tests in the early phase could exclude this limitation; however, it was not feasible to perform multiple tests in critically ill patients soon after SAH and this is made even more difficult as some of the dynamic tests can lead to neurological complications in the early phase after SAH.

In chapter 4, we chose to include patients who survived the acute phase of SAH. Our selection was based on the idea that we wanted to investigate the course of hypopituitarism in the long-term survivors. Not all of our patients had a dynamic test to evaluate GHD. Both these limitations may have led to an underestimation of the total number of patients with PD among which patients with GHD.

Chapter 5 and 6 of this thesis have some limitations too. Firstly, not all measurements were available for all patients. However, most patients could be included in the analysis by estimating the mean outcome using linear mixed model analyses. This statistical method takes into account the covariance between measurements within patients. Secondly, we did not measure other factors that may have affected fatigue and physical

fitness such as depression or anxiety. However, depression and anxiety are not a common feature of PD or GHD[43]. Furthermore, the distribution of depression and anxiety among patients with hypopituitarism and patients with normal pituitary functions after SAH is unknown and therefore their influence on the outcome is disquotable.

Clinical implications and recommendations for future studies.

Although the reported occurrence of hypopituitarism after SAH varies considerably across studies [4, 13, 44], it is evident that PD is a true complication of SAH as our findings confirm the increased occurrence of pituitary dysfunction after SAH.

It is important to consider screening patients for PD as it might have consequences for their long-term outcome.

GH works by directly or indirectly stimulating the production of its tissue effector insulin-like growth factor-1 (IGF-I), which causes different GH changes on peripheral tissues. especially GH/IGF-I axis plays a great part in vascular system. Abnormalities of the GH/IGF-I axis contribute in determining cardiovascular disease, as suggested by clinical studies reporting an increased risk for cardiovascular morbidity and mortality in GHD and it can lead to changes in lipid regulation which also has shown to cause vascular mortality[47, 48]. GH substitution improves body composition and lipid profile, and reduces carotid intima-media thickness at common carotid arteries. It can also improve the cardiac performance, especially peak exercise performance[49-51]. SAH patients have a higher risk for vascular mortality[45]. It is also imaginable that factors which induce atherosclerosis could add to this higher vascular mortality risk[46]. This implicates that we should consider treatment of persistent GHD as this may affect the long-term vascular outcome in these patients.

Fatigue is a frequently reported sequel of SAH. There are a few different pathways to be considered which can trigger fatigue. Changes of neurotransmitter signaling after SAH such as reduced cytokines, substance P, leptin and prostaglandins concentrations and different clinical complications of SAH itself such as hydrocephalus and rebleed can lead to cognitive impairments and fatigue[52-54]. Other factors rather than SAH itself can also play a role in persistence of fatigue in later phase after SAH[53]. Anxiety, mood disturbance such as depression, post-traumatic stress syndrome, sleep disturbance and personality changes can all be seen as important factors that can influence fatigue directly after SAH and in long term after SAH[55-57]. Another enhancing factor for fatigue is the genetic predisposition, which can make subjects more prone for fatigue under conditions of stress and other triggers such as infections. This theory has been described in twin studies with idiopathic chronic fatigue[58]. As fatigue is a common symptom of hypopituitarism, the possible effect of hypopituitarism on fatigue in SAH survivors can be seen as a valuable possible treatable determinant. Keeping this in mind, fatigue after SAH seems to be a multifactorial problem, with one of the factors being hypopituitarism. Screening and treating hypopituitarism among which GHD, might have an effect on the course of fatigue despite of the other variables which also influence fatigue after SAH. Hypopituitarism, when detected, is relatively straightforward to

manage. Screening for hypopituitarism in SAH survivors who remain pathologically fatigued in the long-term should be a consideration which clinicians should be aware of. Long term outcome of SAH survivors also concerns their functional outcome. Physical fitness is important for normal daily functioning[59]. Hypopituitarism has been postulated as a possible determinant of physical fitness[43]. Based on our results, we cannot confirm the association between hypopituitarism and physical fitness.

In conclusion, hypopituitarism is a complication of SAH. Although it is in most cases a self-limiting phenomenon. Therefore, early screening is not obligatory in clinical settings for all patients. Using our screening method, we have established a safe and reliable screening method for hypopituitarism in SAH survivors , which can safely be used for studies. I would recommend screening for pituitary dysfunction at clinical follow-up after SAH only in specific circumstances. Until better predictors of PD become known, patients in whom the level of fatigue does not decrease in the first year after SAH, or seems out of proportion to severity of the SAH, can be selected for screening for hypopituitarism.

Future studies should evaluate the impact of GH replacement therapy on fatigue as the outcome measure, particularly in patients with persistent fatigue. Our observation of physically active patients having a better physical fitness and thereby improving their functional performance indicates the possibility for future research focusing on the effect of tailored and more active rehabilitation programs for SAH survivors to actively enhance their physical fitness and thereby possibly improving their functional outcome.

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Chapter 8

Summary

The introductory **chapter 1** describes the clinical signs and symptoms of subarachnoid hemorrhage (SAH) and hypopituitarism. It provides a short background of current knowledge of the possible association of SAH with hypopituitarism and its possible consequences for outcome after SAH. This chapter explains the rationale of the present study. To better understand the long-term consequences of SAH, we have studied the occurrence of hypopituitarism in patients with SAH, and the effect of hypopituitarism and clinical predictors on fatigue and physical fitness up to 14 months after SAH.

Chapter 2 reviews the literature on the occurrence, possible pattern and severity of endocrine abnormalities. As fatigue, slowness, apathy and decrease in level of activity are common long-term complaints after a SAH and as they resemble the symptoms frequently found in patients with endocrine dysfunction, we attempted to identify risk factors for hypopituitarism after SAH. Pituitary dysfunction may be the direct result of SAH or of its complications such as hydrocephalus or vasospasm. We found the prevalence of endocrine dysfunction to vary from 0 to 55%, and the affected pituitary axes differed between studies. This great variation is due to by differences in patient selection, study design, time elapsed between SAH and endocrine evaluation, different methodology of endocrine tests and definitions of hypopituitarism between the studies. After assessment all the strengths and weaknesses of the studies we concluded that a good quality study was lacking.

In **Chapter 3**, the objective was to determine the diagnostic value of a ghrelin test in the diagnosis of growth hormone deficiency (GHD) shortly after SAH. Therefore, a ghrelin test was carried out after the acute phase within 3 months of SAH and a growth hormone releasing hormone (GHRH) arginine test 6 months post SAH. As ghrelin test is a novel test, we needed a confirmatory test, for which we used GHRH-arginine test. A cut-off limit of a GH peak of 15 μg/L corresponded with a sensitivity of 100 % and a false positive rate of 40% (ROC: 0.869 under the curve). No serious adverse events or idiosyncratic reactions were observed in subjects undergoing a ghrelin test, We concluded that Ghrelin test is a valid and safe test which is also easy to apply in the early phase of SAH.

Chapter 4 describes the incidence and course of pituitary dysfunction (PD) after SAH at baseline, 6 and 14 months and identify clinical determinants for PD in patients with recent SAH.

Almost 40% of SAH survivors in our cohort of 84 patients had PD. In 7% GHD or gonadotropin deficiency persists until at least 14 months. Hydrocephalus is independently associated with PD 6 months after SAH (odds-ratio 3.3 CI 2.7-3.8). Whether SAH patients should be screened for PD is under debate, because clinical significance is not clear. However, there are several reasons to consider early neuro-endocrine evaluation of SAH patients. These concern the possibility of adrenal insufficiency which is life-threatening in the early stressful period after SAH and the possible association with long-term symptoms such as fatigue, low energy level which can influence and hamper the rehabilitation and outcome of these patients.

Chapter 5 describes the possible association between fatigue after SAH and long-term pituitary deficiency in SAH survivors. Fatigue is a common symptom after SAH and in PD, in particular in patients with GHD. Fatigue was measured with the Fatigue Severity Scale (FSS). Seventy six percent of SAH survivors have pathological fatigue directly after SAH and almost 60% of patients still have pathological levels of fatigue after 14 months. There was no effect of PD (p=0.8) or GHD (p=0.23) on fatigue. The Severity of World Federation of Neurosurgical Societies score is a clinical predictor (p=0.008) of fatigue in SAH survivors.

Chapter 6 describes physical fitness in the first year after SAH, its relation with physical activity, sedentary behavior and functional outcome and disease-related characteristics as potential predictors. Physical fitness was assessed by evaluating cardiorespiratory fitness and knee muscle strength. Physical behavior, comprising physical activity and sedentary behavior, were determined by accelerometry-based activity monitoring. The functional independence measure and functional assessment measure were used to evaluate functional outcome. Physical fitness remained very low in more than one-third of the patients over the first year after SAH, and is related to physical inactivity and impaired functional outcome.

The general discussion is **chapter 7** of this thesis. In this chapter the main findings are discussed. At first the relation between hypopituitarism and SAH is discussed. After that the relations between fatigue, physical fitness with SAH and PD are discussed. We take notice of the fact that a large proportion of patients suffer from PD directly after SAH, but this number declines in the first year after SAH. Hypopituitarism does not seem to be the only cause of long-term symptoms of SAH survivors but it can be seen as one of the possible factors that may influence long-term symptoms. Furthermore, the strengths and limitations such as number of participants, observational type of study and incomplete endocrine testing in some cases as well as recommendations for future studies are discussed. We conclude that, based on our findings, screening of all patients early after SAH cannot be recommended. Testing of selected cases can be clinically relevant. Further studies should help define the clinical profile of SAH patients at risk of hypopituitarism.

Samenvatting

Hoofdstuk 1 is een inleidend hoofdstuk welke de kenmerken en symptomen van subarachnoïdale bloeding (SAB) en hypopituïtarisme beschrijft. Dit hoofdstuk biedt een korte samenvatting van de huidige kennis over de mogelijke associatie tussen SAB en hypopituïtarisme en de mogelijke effect en gevolgen van hypopituïtarisme op de lange termijn uitkomst na SAB. In dit hoofdstuk wordt de reden van de huidige thesis uitgelegd. Om de langetermijngevolgen van SAB beter te begrijpen, hebben we het optreden van hypopituïtarisme bij patiënten met SAB en het effect van hypopituïtarisme op vermoeidheid en lichamelijke fitheid tot 14 maanden na SAB bestudeerd.

In **hoofdstuk 2** wordt de literatuur betreffende het voorkomen, het mogelijke patroon en de ernst van endocriene afwijkingen besproken. Hierin zien we dat vermoeidheid, traagheid, apathie en afname van activiteit, veel voorkomende klachten op lange termijn na een SAB zijn en ze lijken op de symptomen die vaak worden gevonden bij patiënten met hypopituitarisme. In dit hoofdstuk hebben we geprobeerd de risicofactoren voor hypopituïtarisme na SAB te identificeren. We zien dat hypopituïtarisme het directe gevolg van SAH kan zijn of het gevolg van de complicaties van SAB zoals hydrocephalus of vasospasme. De prevalentie van endocriene disfunctie varieert tussen 0 en 55% en de aangetaste hypofyse-assen verschilden tussen verschillende onderzoeken. Deze grote variatie is te wijten aan verschillen in selectie van patiënten, onderzoeksopzet, verstreken tijd tussen SAB en de manier van endocriene evaluatie. Verschillende methodologie van endocriene tests en definities van hypopituïtarisme tussen de onderzoeken dragen ook bij aan de gevonden verschillen tussen onderzoeken. Na beoordeling van alle sterke en zwakke punten concludeerden we dat een onderzoek van goede kwaliteit nog ontbrak.

In **hoofdstuk 3** was het doel om de diagnostische waarde van een ghrelin test te bepalen bij het diagnosticeren van groeihormoondeficiëntie (GHD) kort na SAB. Er werd een ghrelin test uitgevoerd binnen 3 maanden na SAB en een growth hormone releasing hormone (GHRH)- arginine test 6 maanden na SAB. Aangezien de ghrelin test een nieuwe test is bij deze groep patiënten, hadden we een bevestigende test nodig, waarvoor we GHRH-arginine-test hebben gebruikt. Een waarde van 15 μg/ L voor groeihormoonpiek kwam overeen met sensitiviteit van 100% en een vals-positief percentage van 40% (ROC: 0,869 onder de curve). Er werden geen ernstige bijwerkingen of idiosyncratische reacties waargenomen bij personen die een ghrelin test ondergingen. Aan de hand van de bevindingen hebben we geconcludeerd dat de ghrelin test een sensitieve en veilige test is, die ook gemakkelijk in de vroege fase van SAH kan worden toegepast voor het vaststellen van GHD.

Hoofdstuk 4 beschrijft de incidentie en het verloop van hypopituïtarisme na SAB binnen 3 maanden en na 6 en 14 maanden en zoeken we naar klinische determinanten voor hypopituïtarisme na SAB.

We zien dat bijna 40% van de overlevenden van SAB in ons cohort van 84 patiënten aan hypopituïtarisme lijdt. Bij 7% blijft GHD of gonadotropine-deficiëntie aanhouden tot minstens 14 maanden na SAB. Hydrocephalus heeft een onafhankelijk associatie met hypopituïtarisme 6 maanden na SAB (odds-ratio 3,3 CI 2,7-3,8). Of SAB-

patiënten moeten worden gescreend op hypopituïtarisme staat ter discussie, omdat klinische betekenis niet duidelijk is. Er zijn echter verschillende redenen om een vroege evaluatie van SAB-patiënten te overwegen. Hierbij moet men denken aan de gevolgen van bijnierinsufficiëntie die levensbedreigend kan zijn in de vroege stressvolle periode na SAB en de mogelijke verband met langdurige symptomen zoals vermoeidheid, laag energieniveau die de revalidatie en de uitkomst van deze patiënten kan beïnvloeden en belemmeren.

Hoofdstuk 5 beschrijft het mogelijke verband tussen vermoeidheid na SAB en hypopituïtarisme bij SAB-patiënten. Vermoeidheid is een veel voorkomend symptoom na SAB en bij hypopituïtarisme, vooral bij patiënten die aan GHD lijden. Vermoeidheid werd gemeten met behulp van Fatigue Severity Scale (FSS). Zesenzeventig procent van de SAB-patiënten heeft een pathologisch niveau van vermoeidheid direct na SAB en bijna 60% van de patiënten heeft na 14 maanden nog steeds pathologische niveaus van vermoeidheid. Er was geen effect van hypopituïtarisme ($p = 0,8$) op vermoeidheid. De World Federation of Neurosurgical Societies score (WFNS) is een klinische voorspeller ($p = 0,008$) van vermoeidheid bij SAB patiënten.

Hoofdstuk 6 is besteed aan de verandering van fysieke fitheid in het eerste jaar na SAB, de relatie met fysieke activiteit, sedentair gedrag, functionele uitkomst en ziekte gerelateerde kenmerken als mogelijke voorspellers van de fysieke fitheid. Fysieke fitheid werd beoordeeld door evaluatie van cardiorespiratoire fitheid en kniespierkracht. Fysiek gedrag, bestaande uit fysieke activiteit en sedentair gedrag, werd bepaald door op activiteit gebaseerde meting. Wat we zagen was dat de fysieke fitheid zeer laag bleef bij meer dan een derde van de patiënten gedurende het eerste jaar na SAB en deze is gerelateerd aan lichamelijke inactiviteit en verminderde functionele uitkomst.

Hoofdstuk 7 betreft de algemene discussie van dit proefschrift. In dit hoofdstuk worden de belangrijkste bevindingen bediscussieerd. Eerst wordt de relatie tussen hypopituïtarisme en SAB besproken. Daarna worden de verbanden tussen vermoeidheid, fysieke fitheid met SAB en hypopituïtarisme besproken. We merken op dat een groot deel van de patiënten direct na SAB aan hypopituïtarisme lijdt, maar gelukkig daalt dit aantal in het eerste jaar na SAB. Hypopituïtarisme lijkt niet de enige oorzaak te zijn van langdurige symptomen van SAB-patiënten, maar het kan worden gezien als een van de mogelijke factoren die de symptomen op lange termijn kan beïnvloeden. Verder worden de sterktes en beperkingen besproken zoals het aantal deelnemers, het observationele type onderzoek en onvolledige endocriene testen in sommige gevallen, evenals aanbevelingen voor toekomstige studies. We concluderen dat, op basis van onze bevindingen, screening van alle patiënten vroeg na SAB niet kan worden aanbevolen. Het testen van geselecteerde gevallen kan klinisch relevant zijn. Verdere studies moeten helpen het klinische profiel van SAB-patiënten met een risico op hypopituïtarisme te definiëren.


9

Chapter 9

Epilogue

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Ik eindig hierbij met 80-87.

About the author | Over de auteur

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Employment, Training and education

Juli 2013	Neurologist Zuyderland MC, Sittard
Dec 2012- june 2013	Neurologist Erasmus MC, Rotterdam

Training

2007-2012	Neurology and Clinical Neurophysiology, Erasmus MC, Rotterdam.
1999-2005	General Medicine, Utrecht
1998-1999	Biology, Utrecht
1991-1997	Gymnasium

List of publications

1: Harmsen WJ, **Khajeh L**, Ribbers GM, Heijenbrok-Kal MH, Sneekes E, van Kooten F, Neggers S, van den Berg-Emons RJ. People With Aneurysmal Subarachnoid Hemorrhage Have Low Physical Fitness and Can Be Predisposed to Inactive and Sedentary Lifestyles.
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2: Harmsen WJ, Ribbers GM, Heijenbrok-Kal MH, **Khajeh L**, Sneekes EM, van Kooten F, Neggers SJCMM, van den Berg-Emons RJ. Fatigue After Aneurysmal Subarachnoid Hemorrhage Is Highly Prevalent in the First-Year Postonset and Related to Low Physical Fitness: A Longitudinal Study.
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3: Hilkens NA, van Asch CJJ, Werring DJ, Wilson D, Rinkel GJE, Algra A, Velthuis BK, de Kort GAP, Witkamp TD, van Nieuwenhuizen KM, de Leeuw FE, Schonewille WJ, de Kort PLM, Dippel DWJ, Raaymakers TWM, Hofmeijer J, Wermer MJH, Kerkhoff H, Jellema K, Bronner IM, Remmers MJM, Bienfait HP, Witjes RJGM, Jäger HR, Greving JP, Klijn CJM; DIAGRAM study group. Predicting the presence of macrovascular causes in non-traumatic intracerebral haemorrhage: the DIAGRAM prediction score.
J Neurol Neurosurg Psychiatry. 2018 Jul;89(7):674-679. doi: 10.1136/jnnp-2017-317262. Epub 2018 Jan 18. PubMed PMID: 29348301.

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J Rehabil Med. 2016 Jun 13;48(6):529-34. doi: 10.2340/16501977-2096. PubMed PMID: 27239762.

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15: **Khajeh L**, Cherian PJ, Swarte RM, Smit LS, Lequin MH. The puzzle of apparent life-threatening events in a healthy newborn.
J Child Neurol. 2014 Jul;29(7):969-72. doi: 10.1177/0883073813481403. Epub 2013 Mar 25. PubMed PMID: 23529910.

16: Blijdorp K, **Khajeh L**, Ribbers GM, Sneekes EM, Heijenbrok-Kal MH, van den Berg-Emons HJ, van der Lely AJ, van Kooten F, Neggers SJ. Diagnostic value of a ghrelin test for the diagnosis of GH deficiency after subarachnoid hemorrhage.
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17: Boerboom W, Heijenbrok-Kal MH, **Khajeh L**, van Kooten F, Ribbers GM. Differences in cognitive and emotional outcomes between patients with perimesencephalic and aneurysmal subarachnoid haemorrhage.
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J Rehabil Med. 2014 Apr;46(4):321-6. doi: 10.2340/16501977-1273. PubMed PMID: 24626873.

PhD Portfolio

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Co-promotor: Dr F. van Kooten/ Dr M.H. Heijenbrok-Kal
Promotor: Prof. Dr. D.W. Dippel/ G. Ribbers

PhD training	**Year**	**Total credits/ hours**
General academic skills		
Biomedical English writing and communication	2013	4
Research skills		
Cardiovascular imaging and diagnostics BROK	2012	7
Various COER courses	2012 and 2018	
Various WMO/ GCP training (online)	2012-2018	
In-depth courses		
Teach the teacher	2013	4.5
Learning courses European stroke conference	2009-2013	
Cardiovascular imaging and diagnostics	2013	
Epiphany meetings	2015	
Basic Clinical Teaching	2017	
Advanced Clinical teaching course	2018	
Presentations		3
Various poster presentations at European stroke conferences	2009-2013	
Various oral presentations		
Seminar neurovascular neurosurgery	2008	
Guideline chronic headache neurology department EMC	2009	
Guideline delirium neurology department EMC	20010	
Guideline post anoxic encephalopathy neurology department EMC	2011	
Guideline epilepsy department of neurology	2012	
Various neurology seminar presentation Zuyderland Medical Center	2013/2019	
International conferences		3
Traumatic brain injury (Rotterdam)	2008	
European stroke conference 2008/2016	2010	
European stroke Organisation Conferenece 2017/2018	2011	
International Vestibular Testing Master Class	2018	
Seminars and workshops		3
Workshop polygraphy and tremor/ transcranial magnetic stimulans	2013	
Neuro-pathology symposium	2010	
Neuro-immunology symposium	2011	
Farmacology symposium	2012	
Epilepsy symposium	2009/2011	
Multiple sclerosis seminar	2010	
Various neurology seminars among which Biemond cursus	2008/2018	
NVKNF dagen	2013/2018	
Work shop extra and intracranial echography	2013/2018	
Other		1
Research meeting neuro-vascular team Rotterdam and regional meeting Regio Limburg	2009-2019	
Teaching activities		
Lecturing		0.5
SSEP (teaching students and interns)	2013/2019	
EEG and epilepsy (teaching students)	2013/2019	
VEP and ERG (teaching interns)	2013/2019	
Neurovascular disease teaching (teaching interns and students)	2013/2019	

Supervising practicals and excursions Multiple neurology practicum and neurophysiology practicum for interns	2013/ 2019	1
Other Supervising multiple student, clinical neurophysiology laborant and several neurology interns(>10)	2011-2019	4
Total ECTS		**30**