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Pituitary dysfunction after aneurysmal subarachnoid hemorrhage is associated with impaired early outcome

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KEY WORDS

Subarachnoid hemorrhage, outcome, hypopituitarism, growth hormone deficiency, pituitary deficiency

ABSTRACT

Objective: Poor outcome and neuropsychological sequelae following aneurysmal subarachnoid hemorrhage (SAH) is a persisting problem. Pituitary dysfunction has been proposed as a contributing factor. Clinical studies have given variable and conflicting results on its importance and incidence after SAH. The aim of this study was to prospectively examine SAH patients with assessment of endocrine function in the acute stage and at early follow-up and to compare clinical SAH features to endocrine abnormalities indicating pituitary dysfunction.

Methods: Endocrine function was assessed by basal hormonal concentrations at 5-10 days and 3-6 months after SAH. Growth hormone deficiency (GHD) was also evaluated by the GHRH-arginine stimulation test at follow-up. Clinical outcome was assessed and scored according to the Glasgow Outcome Scale (GOS).

Results: Fifty-one SAH patients were included and assessed in the acute stage after the bleed. Six were lost to follow-up. The overall prevalence of pituitary dysfunction was 37% and 27% in the acute stage and at follow-up, respectively. Patients with evidence of pituitary dysfunction had significantly worse outcome according to GOS at both occasions. The ruptured aneurysm was more commonly located in the circle of Willis among patients with pituitary dysfunction in the acute stage.

Conclusions: The present results support earlier findings that hormonal abnormalities are not infrequent after SAH. Furthermore, our data suggest that pituitary dysfunction is associated with worse clinical outcome and more common among patients with bleeding sites close to the hypothalamus.

INTRODUCTION

The last few decades have seen great advances in the management of patients with aneurysmal subarachnoid hemorrhage (SAH) with improvements in neuro-intensive care,[8] new technical strategies in treating ruptured aneurysms[5] and advances in monitoring and managing complications such as vasospasm and delayed cerebral ischemia (DCI).[11] Despite this, poor neurological outcome has been reported in as many as 26% of hospital-admitted patients in recent publications.[12] In addition, there have been reports of psychological symptoms, mood disorders, sleep disturbances and mild cognitive sequelae also in patients with good neurological recovery.[21 34 36] This has prompted further investigations of possible factors affecting the clinical course following the bleed. The close anatomical proximity between the usual aneurysm sites and the hypothalamus and pituitary has led to speculation into whether pituitary dysfunction has impact on outcome after SAH.[6] Indeed, some studies have reported endocrine abnormalities indicating pituitary dysfunction following SAH, but the results have been variable and even conflicting.[3 10 16 23-26 31] Parallel to reports on patients with SAH, there have been numerous publications on hypopituitarism following traumatic brain injury.[29] Neuropsychological and cognitive deficits have previously been described in patients with pituitary deficiency caused by other conditions. The profile of neuropsychological impairments related to pituitary deficiency resembles some of those seen after SAH.[4 7 32]

The aim of the present study was to investigate the prevalence of pituitary dysfunction in patients with aneurysmal SAH. The patients were to be prospectively recruited with evaluation of pituitary function by hormonal sampling in the acute stage and follow-up after the bleed. Hormonal abnormalities indicative of pituitary dysfunction were then to be related to clinical features, including extent of hemorrhage seen on CT, location of aneurysm, and clinical status at admission, discharge and follow-up.

METHODS

Patient selection

Patients with aneurysmal SAH treated at the Department of Neurosurgery at the Skåne University Hospital in Lund were recruited for the study from October 2006 until April 2010. Endocrine function was evaluated in the acute stage after SAH and at follow up after 3 to 6 months. Eligible for inclusion were patients with aneurysmal SAH over 18 years of age who could be subjected to endocrine evaluation within 10 days of ictus and at follow-up. Thus, moribund patients were not included. Written, informed consent was obtained from the patient or next-of-kin. Patients for whom this could not be done were excluded. The study was approved by the Regional Ethical Review Board in Lund (65/2006) and registered at the ClinicalTrials.gov database (NCT01101711). As earlier studies had included 30-40 patients with a 37.5-55% prevalence of pituitary dysfunction,[3 10 25] a cohort of 50 was estimated to be a sufficient size.

Treatment and monitoring during the acute stage after SAH

After diagnosis of SAH with suspicion of aneurysmal origin, patients were transferred from local hospitals to the neuro-intensive care unit at our department without delay. Clinical status on admission was graded according to Hunt and Hess.[20] The distribution of blood in the subarachnoid cisterns seen on CT was graded according to Fisher: 1, no blood detected; 2, diffuse SAH < 1 mm thick; 3, diffuse SAH ≥ 1 mm thick; and 4, localized clot in ventricle or parenchyma with or without diffuse SAH.[14] Tranexamic acid was administered to prevent early rebleeds prior to permanent aneurysm occlusion.[18] A ventriculostomy catheter was placed in unconscious patients for monitoring intracranial pressure and to drain cerebrospinal fluid (CSF) in cases of acute hydrocephalus. Aneurysms were permanently secured by either

endovascular embolization (coiling) or open microsurgery (clipping), usually within 24 hours after presentation. During the first 10–14 days after ictus, nimodipine was administered orally to prevent delayed cerebral ischemia. Fluid and electrolyte balance was monitored and patients were kept euvolemic to hypervolemic. Clinically significant hyponatremia (<131 mmol/L)[27] was treated. The cause of hyponatremia following SAH is usually attributed to either cerebral salt wasting (CSW) or syndrome of inappropriate ADH secretion (SIADH).[15] Neurological status was closely monitored as to detect signs of deterioration. Delayed cerebral ischemia was defined as the onset of a neurological deficit or decrease in the level of consciousness (≥2 points on the Glasgow Coma Scale), lasting for at least one hour and not attributable to other causes.[33] Daily measurements of blood flow velocities in the middle cerebral (MCA) and anterior cerebral arteries using transcranial Doppler (TCD) were performed to screen for vasospasm.[1 35] In cases of severe or symptomatic vasospasm, angioplasty either with intra-arterial pharmacological agents, i.e. nimodipine or verapamil, or balloon dilatation was performed.

Assessment of endocrine function

Endocrine evaluation in the acute stage comprised blood samples for morning (9.00 am) plasma levels of FSH, LH, estradiol (in women), testosterone (in men), SHBG, TSH, fT4, ACTH, cortisol, prolactin, Na, K; serum levels of GH and IGF-1, and serum and urine osmolality. Samples were drawn on day 5–10 after ictus. At follow-up after 3 to 6 months, sampling for basal hormone concentrations was repeated, including electrolytes and osmolality. In addition, growth hormone deficiency (GHD) was assessed at follow-up using the GHRH-arginine stimulation test: GHRH (1 μg/kg) and arginine hydrochloride (500 mg/kg) administered intravenously and blood samples drawn after 15, 30, 45, 60, 75 and 90 minutes for GH analysis. Growth hormone deficiency was defined as a peak GH response of

<11 µg/L in patients with Body Mass Index (BMI) <25 kg/m^2, <8 µg/L in patients with BMI 25–30 kg/m^2 and <4 µg/L in patients with BMI >30 kg/m^2.[19]

Assessment of adrenocorticotropic function was based on unstimulated cortisol levels. For interpretation, cut-off levels were set at 100, 250 and 450 nmol/L. These levels were chosen since basal cortisol levels <100 nmol/L have been reported to be associated with subnormal ACTH function and that levels >450 nmol/L almost never have been associated with central hypoadrenalism.[17] In between these, 250 nmol/L was used as the level to distinguish cases of suspected deficiency from those with probable normal function.[9]

Reference values for the other hormonal analyses were; FSH: 1.7-22 IE/L for premenopausal women, 25-135 IE/L for postmenopausal women, 1.5-13 IE/L for men; LH: 1.0-96 IE/L for premenopausal women, 7.7-59 IE/L for postmenopausal women, 1.7-8.6 IE/L for men; estradiol: 90-1500 pmol/L for premenopausal women, <150 pmol/L for postmenopausal women; testosterone: 7.6-31 nmol/L for men <50 years, 4.6-31 nmol/L for men >50 years; SHBG: 14-48 nmol/L; TSH: 0.40-4.0 mIE/L; fT4: 12-22 pmol/L; ACTH: 1.0-13 pmol/L; prolactin: 3-22 µg/L; Na: 136-146 mmol/L; K: 3.2-4.7 mmol/L; IGF-1: 116-358 µg/L for age 21-25 years, 117-329 µg/L for age 26-30 years, 115-307 µg/L for age 31-35 years, 109-284 µg/L for age 36-40 years, 101-267 µg/L for age 41-45 years, 94-252 µg/L for age 46-50 years, 87-238 µg/L for age 51-55 years, 81-225 µg/L for age 56-60 years, 75-212 µg/L for age 61-65 years, 69-200 µg/L for age 66-70 years, 64-188 µg/L for age 71-75 years, 59-177 µg/L for age 76-80 years; and serum osmolality: 280-300 mosmol/kg.

The present hormonal data were all collected for study purposes and not on clinical indications. From the clinical point of view, none of the patients were considered for hormonal substitution.

Clinical outcome

Neurological outcome was evaluated using the Glasgow Outcome Scale (GOS)[22] at discharge from the department of neurosurgery, usually 10 to 15 days after admission, and at a follow-up visit 3-6 months later in the out-patient clinic according to study protocol. The evaluation was performed blinded to the endocrine data by two of us (EK or OGN).

Statistical analysis

Statistical analyses were performed using SPSS Statistics v. 20 (IBM Corp.). The Mann-Whitney U test was used for group comparisons of age, Hunt and Hess grade, Fisher grade and GOS. Fisher's exact test was used for binary outcome parameters. P values $< .05$ were considered statistically significant.

RESULTS

Study population

Patients with aneurysmal SAH were screened with 60 fulfilling inclusion criteria. For two patients, informed consent could not be obtained. Seven patients declined participation, leaving 51 to be tested in the acute stage. At follow up, consent for further endocrine evaluation had been withdrawn for 4 patients, all of which were GOS 2 or 3. One patient had died from a new SAH caused by an aneurysm other than the previously ruptured and treated. One patient could not be summoned for follow up examinations within the set time frame due to other health problems, leaving 45 patients eligible for follow-up examinations (Figure 1).

Clinical SAH characteristics

Clinical findings at presentation among 51 patients are given in Table 1. None of the patients were in Hunt and Hess grade 5 at admission. All patients had SAH visible on CT (Fisher grade 2 - 4). Presence of an aneurysm was confirmed by CT or catheter angiography in all

cases. Aneurysms were located in the circle of Willis (ACoA, PCoA, AChA, ICA bifurcation or basilar apex) in close proximity of the hypothalamus and the pituitary stalk in 78% of patients. Other locations were middle cerebral artery (MCA) bifurcation (16%) and pericallosal artery (6%). All ruptured aneurysms were occluded by endovascular coiling (75%) or surgical clipping (25%). There were no rebleeds between admission and permanent aneurysm occlusion. Hydrocephalus in the early phase, requiring external ventricular drainage, was seen 13 patients (25%). Need for long-term CSF drainage requiring a ventriculoperitoneal shunt occurred in nine (18%). Neurological deterioration due to delayed cerebral ischemia was seen in 10 cases (20%). In 17 patients (33%), TCD detected blood flow velocities in MCA over 120 cm/s suggesting vasospasm. Endovascular angioplasty was performed in six patients with symptomatic cerebral vasospasm.

The clinical course was favorable for most patients; status as measured by GOS at discharge from the neurosurgical department was 4 in 30 patients, 3 in 19, and 2 in two patients. At the time of follow-up, GOS scores were 5 in 27 patients, 4 in 17, 3 in five, 2 in one and 1 in one (Table 2).

Prevalence of endocrine abnormalities

Adrenal axis

In the acute stage, four patients (8%) had plasma cortisol levels <250 nmol/L indicating adrenocorticotropic deficiency. At follow-up eight patients (18%) had cortisol levels indicating deficiency (Figure 2).

Thyroid function

Elevated TSH concentrations indicating primary hypothyroidism were seen in three patients in the acute stage and in one at follow up. Two patients had thyroxine replacement therapy

from before SAH. Thus, their data did not reflect possible thyrotrophic dysfunction. Three patients (6%) had normal TSH levels in spite of low fT4 levels, indicating insufficient thyrotrophic function in the acute stage. At follow up this was seen only in one patient (2%) (Figure 2).

Somatotropic function

Low concentrations of IGF-1 were seen in six patients (12%) in the acute stage and in nine patients (20%) after 3–6 months. Dynamic assessment at follow-up using the GHRH-arginine stimulation test revealed three responses indicating GHD (7%). These three individuals all had low IGF-1 levels (Figure 2).

Gonadotropins

The gonadotropin axis was evaluated by measuring LH and FSH levels. Estradiol was also measured in women and testosterone in relation to SHBG levels in men. In the acute phase, 15 patients (30%; 13 female and two male) had low gonadotropin levels indicating secondary hypogonadism, but at follow up this was seen only in two (4%; both female; Figure 2).

Antidiuretic hormone

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

Prolactin

Mild hyperprolactinemia (<35µg/L) was seen in eight patients in the acute phase and in one at follow-up.

Development over time

Only four patients had endocrine abnormalities in the acute stage that persisted at follow-up (patients no. 8 – cortisol, 14 – FSH/LH, 32 – GH and FSH/LH, and 46 – FSH/LH; Table 3). In all other cases, the abnormalities had either resolved or were new at the time of follow-up.

Pituitary dysfunction in relation to clinical SAH features

Acute stage endocrine evaluation. Nineteen patients (37%) were diagnosed with pituitary dysfunction of one or more axes in the acute stage (mild hyperprolactinemia and hyponatremia not included). These patients showed a significantly less favorable clinical outcome as measured by GOS at discharge compared to those with normal pituitary function (Mann-Whitney U test; $p = 0.018$). This difference did not persist at follow up for these patients ($p = 0.12$). Patients with pituitary dysfunction in the acute stage were also significantly more likely to have had a ruptured aneurysm in the circle of Willis (Fisher's exact test; $p = 0.037$) and to have their aneurysm treated by coiling (Fisher's exact test; $p = 0.018$; Table 4).

Follow-up endocrine evaluation. Twelve patients (27%) developed or had persisting pituitary dysfunction at follow up (with GHD defined by GHRH-arginine testing rather than IGF-1 levels alone). These patients were significantly younger than those with normal pituitary function (Mann-Whitney U test; $p = 0.006$). No other baseline clinical feature, including GOS at discharge, differed between these groups. However, clinical outcome at follow up as measured by GOS was less favourable in patients with pituitary dysfunction (Mann-Whitney U test; $p = 0.041$; Table 4).

DISCUSSION

In the cohort of SAH patients followed in this study, pituitary deficiency in at least one axis was seen in 37 % in the acute stage and in 27 % at early follow-up 3-6 months after hemorrhage. This prevalence of endocrine disturbances is consistent with previous studies by Dimoupolou et al,[10] Kreitschmann-Andermahr et al,[25] Aimaretti et al[3] and Tanriverdi et al[31] (37.5-68.2% prevalence at follow-up), but contrasts to results from Klose et al[24] and Lammert et al[26] who found few or no abnormalities at confirmatory testing. Gardner et al[16] recently reported 12% hypopituitarism in their patient series, however also with non-aneurysmal SAH patients included. The German Database on Hypopituitarism after Traumatic Brain Injury and Aneurysmal Subarachnoid Hemorrhage has also revealed a similar incidence of pituitary dysfunction.[30] However, these data have not been collected within a defined study protocol. To date, the present study is the largest single-center study to prospectively evaluate endocrine function among exclusively aneurysmal SAH patients both in the acute stage after ictus and at later follow-up. There was a selection bias towards good clinical grade patients. This is consistent with all the similar studies mentioned above, and may reflect difficulty in obtaining consent from poor grade patients for this kind of follow-up. There was also a selection bias toward more female patients. This is unlikely to have impact on the results, as there were no differences in incidence of pituitary dysfunction between males and females.

Hormonal abnormalities after SAH by axis

Adrenocorticotropic function was assessed indirectly by measuring morning (9 am) levels of cortisol. The cut-off value of 250 between suspected deficiency and probable normal function

has been proposed by Courtney et al.[9] By this definition, 8% had cortisol levels indicating impaired adrenocortical function in the acute stage and 18% at follow-up. The incidences previously reported have varied from 0 to 40%. The most extreme findings have been made by dynamic testing with the insulin tolerance test (ITT).[24 25]

Subnormal levels of fT4 without appropriate elevation of TSH were interpreted as indicative of thyrotrophic deficiency. This was seen in 6% in the acute stage and 2% at follow-up. This is in accordance with previous studies, which have consistently reported low incidences of TSH deficiency with the exception of Aimaretti et al (9.3%).[3]

For the assessment of somatotropic function, IGF-1 levels were used as a biochemical marker. However, IGF-1 levels also depend on other factors, such as nutritional status. Thus, a malnourished patient may have low IGF-1 levels also without GHD. The ITT is the gold standard for testing GHD.[19] However, induction of hypoglycemia poses known risks of aggravating or eliciting epilepsy and ischemic heart disease.[13] For the participants of this study with recent history of SAH, ITT was considered too riskful to be employed. At follow-up, the GHRH-arginine stimulation test with cut-off levels adapted according to individual BMI was used instead. This test is well validated in adults,[19] but acts by directly stimulating the pituitary gland leaving the risk of giving false normal results in case of local hypothalamic injury. Our finding of 12% with low IGF-1 levels in the acute stage may be an overestimate of GHD, but the 7% with low IGF-1 and pathologic responses to GHRH-arginine stimulation likely represent impaired GH secretion at follow-up. This is a lower prevalence than reported in most studies, in which GHD often has been the most commonly affected endocrine axis (20-37%),[3 10 23 25 31] although two studies report no incidence of GHD at all.[24 26]

Gonadotropin deficiency was the most common endocrine abnormality in the acute stage (30%) but was less common at follow-up (4%). This pattern has also been

described after traumatic brain injury and has been argued to be a part of a more general response to severe acute illness.[2] Similar findings following SAH with high incidences in the acute stage that later resolves has also been demonstrated by Tanriverdi et al[31] and Klose et al.[24]

In most cases, pituitary impairments were either new or had resolved at follow-up compared to the acute stage. Similar findings have also been noted in longitudinal studies by Aimaretti et al,[3] Tanriverdi et al[31] and Karaca et al.[23] As stated above, acute phase abnormalities that later resolves may be a transient functional response, but may also represent the restorative capacity of the hypothalamic structures involved. On the other hand, endocrine abnormalities that become apparent in later phases, may initially have been masked by an acute neuroendocrine response to severe disease or may represent delayed secondary injury mechanisms. Whereas no differences in study design seem to explain the divergent findings on the incidence of pituitary dysfunction in this and other studies, this variability over time may contribute to the conflicting data reported.

Pituitary dysfunction in relation to SAH features

In relating endocrine abnormalities to clinical features, we chose to compare differences between patients with normal pituitary function to all those with dysfunction in one or more axis. To make comparisons axis by axis would have yielded too small groups to give meaningful results. Patients with pituitary dysfunction in the acute stage were significantly more likely to have SAH from an aneurysm in the circle of Willis (ACoA, PCoA, AChA, ICA bifurcation or basilar apex) than other locations (MCA or pericallosal artery). This is likely due to the close anatomical relationship between the circle of Willis and the hypothalamus and pituitary stalk. Furthermore, patients with hypopituitarism were more likely to have had their aneurysms treated by endovascular technique. This is at least in part due to a propensity

to coil basilar apex and to clip MCA aneurysms and thus biased by location. At follow-up these differences in aneurysm location and treatment modality were not seen. Comparisons of endocrine dysfunction between patients with ruptured aneurysms in the circle of Willis versus other locations have not been presented before.

GOS was chosen for assessment of clinical outcome. Although initially designed for trauma follow up, it has been used frequently for SAH patients.[5] GOS can be seen as too blunt to detect smaller differences in cognitive function and physical ability that usually are attributed to endocrine dysfunction. On the other hand, the dichotomy of poor versus good outcome is a common way of presenting outcome after stroke. We have presented comparisons of medians. Interestingly, we found that pituitary abnormalities in the acute stage were associated with a lower median GOS score at discharge but not at follow-up. By then, most hormonal abnormalities in this group of patients had resolved. Conversely, pituitary dysfunction at follow-up was associated with lower median GOS at follow-up but not at discharge. In the acute stage the majority of patients in this group had no endocrine abnormalities, lending further support to a correlation between outcome and pituitary function. Data on outcome in relation to hormonal abnormalities have been presented earlier,[10 25] but significant differences between patients with normal and impaired endocrine function have not been reported.

At follow-up, patients with pituitary dysfunction were significantly younger than those with normal function. This was also found to be the case in the 12 month post-SAH evaluation by Gardner et al.[16]

The strength of our study is the prospective design, the broad endocrine evaluation and the correlation of endocrine disturbances to clinical characteristics of SAH. Shortcomings could be the number of patients with some lost to follow-up assessment of hormonal function. Earlier studies had included 30-40 patients.[3 10 25] By expanding this to

a cohort of 50, we considered the sample size to be sufficient to yield scientifically relevant data.

As demonstrated previously and in the present study, the endocrine panorama seems to shift over time, in a way that, according to our new data, is of importance for the clinical outcome. This underlines the need of close follow-up and endocrine re-evaluation. The patients in this cohort are to be re-investigated for pituitary function. This will include endocrine assessment 1-2 years after the bleed with additional dynamic testing of somatotropic and adrenocorticotropic function. This will serve as confirmatory testing of the present early results and further elucidate possible long-term endocrine consequences of SAH. Guidelines for screening SAH patients for endocrine dysfunction are as yet to be established. Further follow-up will be helpful in deciding which patients to examine and when to do it. Based on studies on hypopituitarism following traumatic brain injury, a proposal for guidelines regarding follow-up assessment of endocrine function after brain trauma has recently been published in Sweden.[28]

CONCLUSIONS

The present results support earlier findings that pituitary dysfunction occurs frequently after aneurysmal SAH. Furthermore, we have demonstrated that pituitary dysfunction was associated with less favorable outcome, both early in the course of events and later, at follow-up after 3-6 months. Pituitary dysfunction in the acute stage was more common in patients with ruptured aneurysms in the circle of Willis compared to other sites, suggesting direct injury from the bleed to hypothalamic structures as the pathogenic mechanism.

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Figure 1 Flow chart of patients excluded from the study.

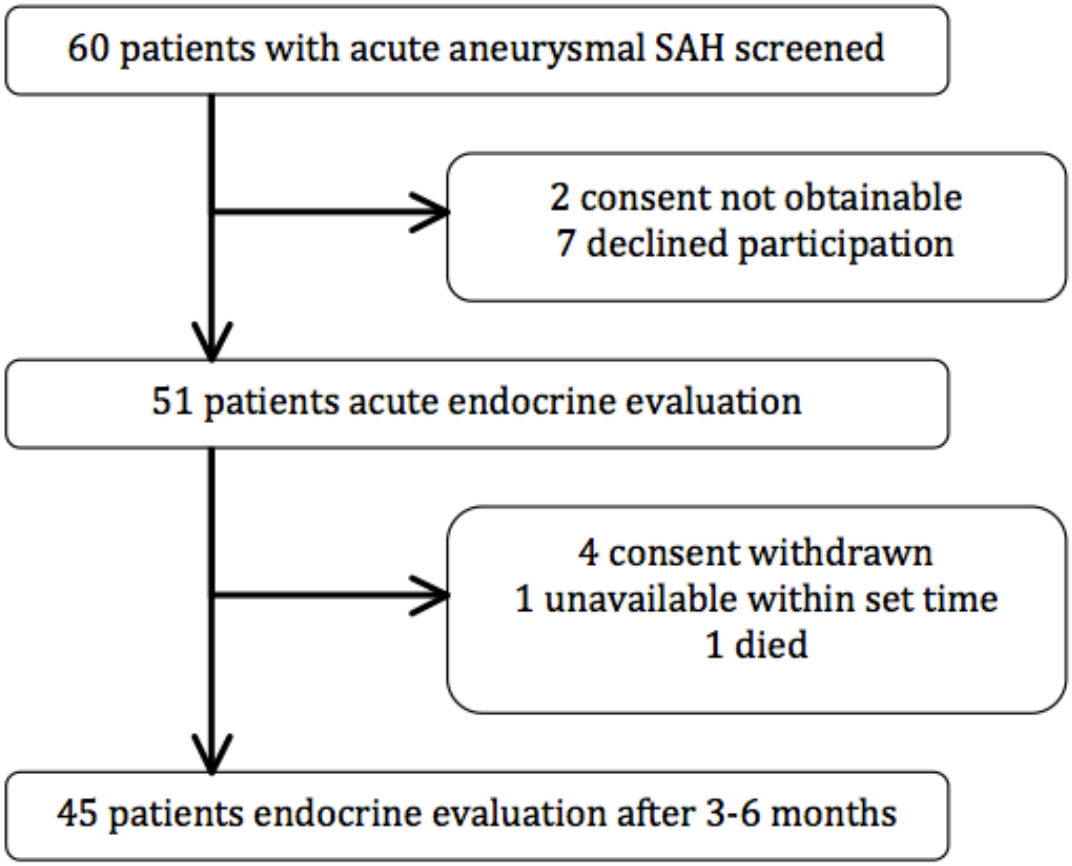

Figure 2 Percentages of subarachnoid hemorrhage patients with pituitary dysfunction by axis in the acute stage and at 3-6 months follow-up. Growth hormone deficiency defined by IGF-1 at both times, but defined by GHRH-arginine stimulation test at follow-up only. GH = growth hormone; GHRH = growth hormone releasing hormone IGF-1 = insulin-like growth factor 1.

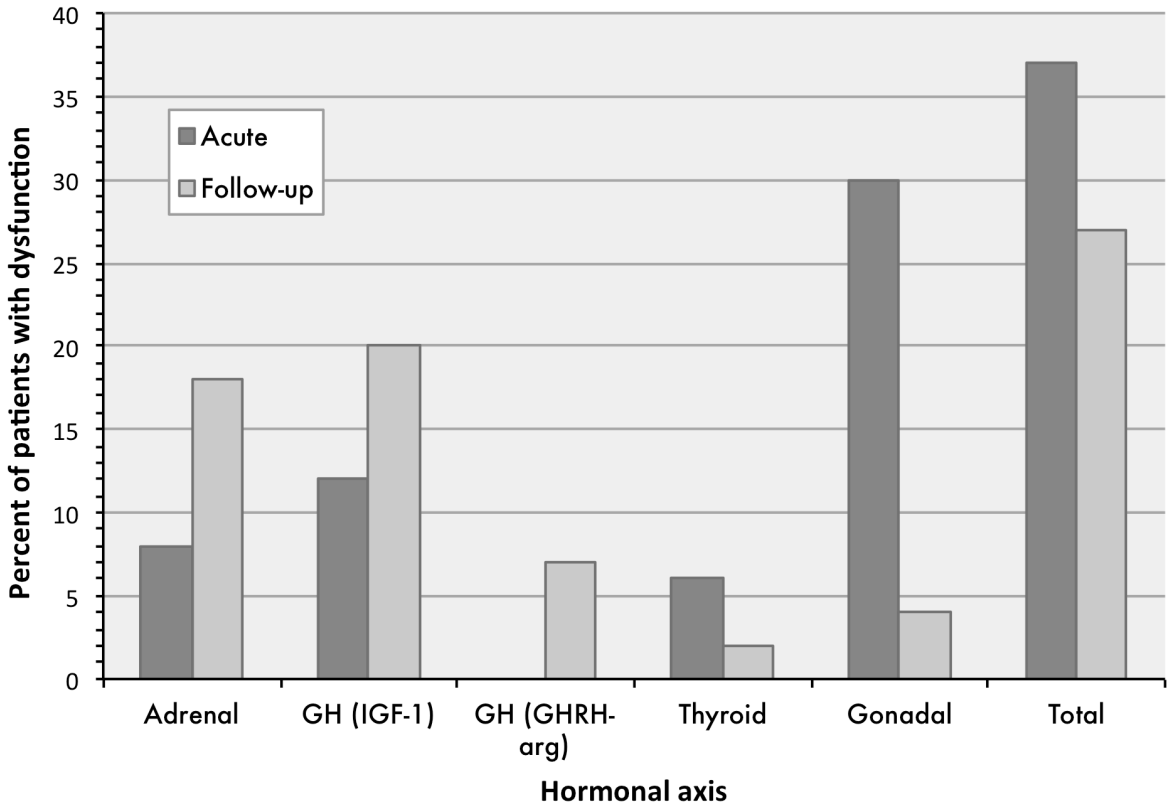

Table 1 Baseline data and clinical events related to SAH (n = 51) [a]

Median age, years (range)		55 (28-75)
Female gender		43 (84%)
Aneurysm location		
Circle of Willis		40 (78%)
	ICA (PCoA, AChA, ICA bifurcation)	17 (33%)
	ACoA	20 (39%)
	Basilar apex	3 (6%)
Other		11 (22%)
	MCA	8 (16%)
	Pericallosal	3 (6%)
Hunt & Hess grade		
	1: Asymptomatic/mild headache	6 (12%)
	2: Moderate/severe headache	21 (41%)
	3: Drowsiness/confusion	17 (33%)
	4: Stupor	7 (14%)
	5: Coma/decerebrate posturing	0
Fisher grade		
	1: No blood detected	0
	2: Diffuse SAH, < 1mm thick	8 (16%)
	3: Diffuse SAH, ≥ 1mm thick	28 (55%)
	4: Clot in ventricle or parenchyma	15 (29%)
Treatment modality		
	Endovascular (coiling)	38 (75%)
	Surgery (clipping)	13 (25%)
Hydrocephalus		
	External ventricular drainage	13 (25%)
	Ventriculoperitoneal shunt	9 (18%)
Delayed cerebral ischemia		10 (20%)
Vasospasm		
	TCD > 120	17 (33%)
	Angioplasty	6 (12%)

[a]AChA = anterior choroidal artery; ACoA = anterior communicating artery; ICA = internal carotid artery; MCA = middle cerebral artery; PCoA = posterior communicating artery; SAH = subarachnoid hemorrhage; TCD = transcranial Doppler
's exact test

Table 2 Neurological outcome according to Glasgow Outcome Scale (GOS; n=51)

GOS	at discharge	at follow-up[a]
5: Good recovery	0	27 (53%)
4: Moderate disability	30 (59%)	17 (33%)
3: Severe disability	19 (37%)	5 (10%)
2: Vegetative state	2 (4%)	1 (2%)
1: Death	0	1 (2%)

[a]Note that at follow-up after 3-6 months, consent for further endocrine investigations had been withdrawn for three patients with GOS 3 and one patient with GOS 2. One patient with GOS 3 could not be summoned within the set time-frame and neither could one patient with GOS 1.

Table 3 List of patients with pituitary dysfunction in the acute stage and at follow-up after 3-6 months, by axis; (+) indicates dysfunction and (-) indicates normal function

Pat.no	Age[a]	Gender	Adrenal		Thyroid		Somatotropic[b]		Gonadal		Any axis	
			Acute	F/U	Acute	F/U	Acute	F/U	Acute	F/U	Acute	F/U
1	58	Female	+	-	-	-	+	-	-	-	+	-
3	62	Female	-	-	-	-	-	-	+	-	+	-
5	64	Female	-	-	+	-	+	-	+	-	+	-
6	52	Female	-	+	-	-	-	-	-	-	-	+
8	42	Female	+	+	-	-	-	-	+	-	+	+
10	48	Female	-	+	-	-	-	-	-	-	-	+
11	47	Female	-	-	+	-	-	-	+	-	+	-
12	50	Female	-	-	-	-	-	-	+	-	+	-
14	49	Female	+	-	-	-	-	-	+	+	+	+
15	39	Female	-	+	-	+	-	-	-	-	-	+
17[c]	61	Male	-	N/A	-	N/A	+	N/A	+	N/A	+	N/A
21	39	Female	-	-	-	-	-	+	-	-	-	+
23	61	Male	-	-	-	-	-	-	+	-	+	-
24	50	Female	-	+	-	-	-	-	-	-	-	+
27	65	Female	-	+	-	-	-	-	-	-	-	+
29	44	Female	-	-	-	-	-	-	+	-	+	-
32	67	Female	-	-	-	-	+	+	-	-	+	+
34	64	Female	-	-	-	-	-	-	+	-	+	-
37	49	Male	-	+	-	-	-	+	-	-	-	+
38	48	Female	+	-	-	-	-	-	-	-	+	-
40	68	Female	-	-	-	-	-	-	+	-	+	-
42	52	Female	-	+	+	-	-	-	-	-	+	+
45	52	Female	-	-	-	-	-	-	+	-	+	-
46	29	Female	-	-	-	-	+	-	+	+	+	+
47[c]	73	Male	-	N/A	-	N/A	-	N/A	+	N/A	+	N/A
49[c]	45	Female	-	N/A	-	N/A	+	N/A	+	N/A	+	N/A

[a]Age at time of SAH

[b]Somatotropic function assessed by IGF-1 concentrations in the acute stage and by IGF-1 and GHRH-stimulation test at follow-up

[c]N/A, not available; there was no follow-up endocrine evaluation of patients 17, 47 and 49

F/U, follow-up

Table 4 Clinical features of patients with dysfunction in one or more pituitary axis compared to those with normal pituitary function in the acute stage and at follow up after 3 to 6 months (note that there was no endocrine evaluation in six patients at follow-up)

		Acute stage endocrine evaluation		Follow-up endocrine evaluation	
		Normal (n=32)	**Dysfunction (n=19)**	**Normal (n=33)**	**Dysfunction (n=12)**
Median age, years (range)		56 (39–75)	51 (28–73)	59 (41–75)	49 (28–66)[b]
Female gender		27 (84%)	16 (84%)	29 (88%)	10 (83%)
Aneurysm location					
	Circle of Willis/other[a]	22(69%)/10(31%)	18(95%)/1(5%)[c]	26(79%)/7(21%)	9(75%)/3(25%)
Hunt & Hess					
	1: Asymptomatic/mild headache	4 (13%)	2 (11%)	3 (9%)	1 (8%)
	2: Moderate/severe headache	14 (44%)	7 (37%)	16 (48%)	5 (42%)
	3: Drowsiness/confusion	11 (34%)	6 (32%)	10 (30%)	6 (50%)
	4: Stupor	3 (9%)	4 (21%)	4 (12%)	0
	5: Coma/decerebrate posturing	0	0	0	0
	Median Hunt & Hess	2	3	2	2
Fisher grade					
	1: No blood detected	0	0	0	0
	2: Diffuse SAH, < 1mm thick	5 (16%)	3 (16%)	5 (15%)	2 (17%)
	3: Diffuse SAH, ≥ 1mm thick	18 (56%)	10 (53%)	18 (55%)	9 (75%)
	4: Clot in ventricle or parenchyma	9 (28%)	6 (32%)	10 (30%)	1 (8%)
	Median Fisher	3	3	3	3
Treatment modality					
	Coiling/Clipping	20(62%)/12(38%)	18(95%)/1(5%)[c]	25(76%)/8(24%)	8(67%)/4(33%)
Hydrocephalus					
	External ventricular drainage	7 (22%)	6 (32%)	9 (27%)	1 (8%)
	Ventriculoperitoneal shunt	3 (9%)	6 (32%)	6 (18%)	1 (8%)
Delayed cerebral ischemia		5 (16%)	5 (26%)	6 (18%)	1 (8%)
Vasospasm					
	Transcranial Doppler	9 (28%)	8 (42%)	8 (24%)	5 (42%)
	Angioplasty	3 (9%)	3 (16%)	3 (9%)	1 (8%)
Glasgow Outcome Scale (GOS) at discharge					
	5: Good recovery	0	0	0	0
	4: Moderate disability	23 (72%)	7 (37%)	20 (61%)	9 (75%)
	3: Severe disability	8 (25%)	11 (58%)	12 (36%)	3 (25%)
	2: Vegetative state	1 (3%)	1 (5%)	1 (3%)	0
	1: Death	0	0	0	0
	Median GOS	4	3[b]	4	4
GOS at follow up					
	5: Good recovery	20 (62%)	7 (37%)	23 (70%)	4 (33%)
	4: Moderate disability	8 (25%)	9 (47%)	9 (27%)	8 (67%)
	3: Severe disability	3 (9%)	2 (11%)	1 (3%)	0
	2: Vegetative state	0	1 (5%)	0	0
	1: Death	1 (3%)	0	0	0
	Median GOS	5	4	5	4[b]

[a] Middle cerebral or pericallosal arteries

[b] $p < 0.05$, Mann-Whitney U test

[c] $p < 0.05$, Fisher's exact test