

**Research paper**

## **Neuroendocrine dysfunction in patients recovering from subarachnoid hemorrhage**

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### **ABSTRACT**

**OBJECTIVE:** Subarachnoid hemorrhage (SAH) is a recently identified risk factor for hypopituitarism, particularly growth hormone (GH) and corticotrophins deficiencies. The aim of our study was to identify possible predictor(s) for neuroendocrine dysfunction in SAH survivors. **DESIGN:** Pituitary function was evaluated in 93 patients (30 males, 63 females), aged  $48.0 \pm 1.1$  years (mean  $\pm$  SE), and with a Glasgow Outcome Scale score of  $4.6 \pm 0.6$  (mean  $\pm$  SE) more than one year following SAH. In the acute phase, SAH was complicated by vasospasm (VS) in 18 and by hydrocephalus (HDC) in 9 patients. Baseline serum values of Insulin Growth Factor 1 (IGF-I), cortisol, Thyroxine (T4), Thyroid Stimulating Hormone (TSH), Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), testosterone (in males), estradiol (in females) and prolactin were determined. **RESULTS:** According to the results of baseline hormonal evaluation, 47 patients (50.5%) had no hormonal abnormalities. Seven patients (7.5%) had multiple pituitary hormone deficiencies: Four patients (4.3%) had two (GH and cortisol), one patient had three (gonadal, adrenal and GH) and two patients had deficiency of all pituitary axes. Thirty-nine patients (42%) had one abnormal axis (13 adrenal, 2 thyroid, 4 gonadal and 20 GH). None of the subjects was treated with desmopressin or exhibited symptomatic polyuria. The VS and HDC during the acute phase of SAH were related to abnormal pituitary status (VS with low IGF-I levels and HDC with low cortisol levels). **CONCLUSION:** Through a screening procedure, neuroendocrine dysfunction was identified in a substantial number of asymptomatic patients with previous SAH. Cerebral VS and HDC at the time of SAH emerged as risk factors possibly predicting development of pituitary dysfunction. Low basal levels of IGF 1 and cortisol may help in selecting patients requiring further evaluation of pituitary function.

**Key words:** Cerebral aneurysm, Hypopituitarism, Subarachnoid hemorrhage, Traumatic brain injury

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*Received 04-02-10, Revised 10-04-10, Accepted 10-05-10*

## INTRODUCTION

Recent studies provide evidence for a high prevalence of neuroendocrine dysfunction in subarachnoid hemorrhage (SAH) survivors ranging from 27.5% to 55%.<sup>1-6</sup> Pituitary insufficiency in a patient after SAH caused by the rupture of an aneurysm of the anterior communicating artery was published in 1961 by Hoff et al.<sup>7</sup> Kelly and colleagues reported pituitary insufficiency after SAH in two patients 3.5 and 13 months, respectively, after aneurysmal SAH.<sup>1</sup> These patients presented with Growth Hormone Deficiency (GHD) diagnosed by Insulin Tolerance Test (ITT). Recent reports indicate a high prevalence of pituitary and hypothalamic abnormalities following SAH and TBI.<sup>1-6,8</sup> It is still unclear whether the observed cognitive deficits are a consequence of the brain injury itself or are also related, at least in part, to the resulting anterior pituitary hormone deficiencies.

SAH shares some clinical features with traumatic brain injury (TBI), such as the loss of consciousness and amnesia. The pattern of cognitive and behavioral consequences of SAH are similar to those of TBI as well as of partial or complete pituitary insufficiency.<sup>9</sup> Adult patients with GHD of non-SAH and non-TBI origin complain of attention and memory decline in spite of adequate adrenal, thyroid or sex hormone replacement therapy.<sup>10-12</sup> The GH replacement therapy in these patients led to significant improvement of long- and short-term memory and cognitive functions.<sup>11</sup>

SAH accounts for about 5-10% of all strokes in people around 50 years of age, with the estimated annual incidence rate at between 10 to 25 cases per 100,000.<sup>13</sup> The risk factors for aneurysmal SAH are hypertension and cigarette smoking.<sup>13</sup> SAH is fatal in more than half of the cases and serious disability is common among survivors.<sup>14</sup> Modern management has reduced mortality and disability by about 30% compared with 30 years ago. Despite a good neurological outcome, patients surviving SAH frequently present with persistent cognitive and behavioral impairment.<sup>15,16</sup> Over half showed clinically significant post-traumatic stress symptomatology at three months and 30% at nine months following SAH.<sup>17</sup> Cognitive sequelae are most prominent in the domains of memory (visual short-term and verbal long-term),

reaction-time task, concentration and nomination.<sup>18</sup> These consequences of SAH significantly affect the recovery and quality of life of patients and their families. Life-satisfaction and motivation are reduced, while emotional lability is increased.<sup>18</sup> In the study of Bjeljac and colleagues, almost all patients presented with good neurological status [Glasgow Outcome Scale (GOS) score 4] one year after SAH, but only 30% exhibited no neuropsychological deficit.<sup>19</sup>

According to recently published recommendations for GH testing, patients who have survived traumatic brain injury and subarachnoid hemorrhage are included in the population who require evaluation of the hypothalamo-pituitary axes.<sup>20-22</sup>

We undertook the present pilot study to diagnose patients with increased risk for neuroendocrine dysfunction following SAH as well as to identify possible predictor(s) of neuroendocrine dysfunction.

## PATIENTS AND METHODS

### *Patients*

Long-term consequences of adult SAH survivors were studied by a team comprised of neurosurgeons and endocrinologists. The inclusion criteria for the study were: 1) history of aneurysmal SAH, 2) age 18 to 70 years at the time of testing, 3) time elapsed from the SAH between 1 and 10 years, and 4) good outcome after the hemorrhage, namely a GOS score of 4 to 5. The exclusion criteria were: 1) history of severe depression (known to alter cortisol secretion) and 2) history of severe liver disease, kidney disease or uncontrolled diabetes mellitus.

Diagnosis of SAH was confirmed by computerized tomography (CT) scanning or lumbar puncture, and aneurysm location was determined by angiography (anterior communicating artery-ACoA, middle cerebral artery-MCA, internal carotid artery-ICA, vertebrobasilar artery-VBA). All patients were surgically treated. Hydrocephalus and cerebral vasospasm were considered as acute complications, while epilepsy was considered as a chronic complication of SAH.

Ninety-three SAH patients conforming to the inclusion and exclusion criteria were enrolled in the study. Body weight and height were measured and body mass index (BMI) was calculated. The previously

known risk factors for SAH were recorded (arterial hypertension, smoking habits, diabetes mellitus). The study was approved by the hospital Ethics Committee and informed consent was obtained from all patients for the endocrine testing.

### **Hormonal testing and assays**

Serum samples for insulin-like growth factor I (IGF-I), thyroxine (T4), TSH, FSH, LH, prolactin and cortisol determination were taken after an overnight fast, at 08:00. Serum total testosterone was determined in all males and serum estradiol in females. A menstrual history was taken in all female subjects. All samples were stored at -80°C until assayed.

Hormones were measured by commercial kits: T4 by RIA (INEP, Zemun, Serbia). TSH by IRMA (INEP, Zemun, Serbia). PRL, LH and FSH by IRMA (Cis BioInternational, France). Cortisol, testosterone and estradiol were measured by RIA (Cis BioInternational, France). IGF-I was measured by chemiluminescent enzyme immunoassay with the Immulite Analyzer (Diagnostic Product Corporation, Los Angeles, CA, USA).

### **Data analysis**

The standard reference ranges were used to discriminate abnormal from normal results of T4, TSH, basal cortisol, prolactin, FSH, LH, testosterone (in males) and estradiol (in females). Age- and gender-specific normal ranges were used for interpreting IGF-I levels. Menses within the past 42 days were considered normal.

Secondary hypocortisolism was diagnosed if morning serum cortisol level was less than 131 nmol/l. TSH deficiency was defined as a low T4 level in the presence of an inappropriately low TSH level. In males, diagnosis of gonadotrophin deficiency was based on a low testosterone level in the presence of normal PRL and normal or low levels of gonadotrophins. In premenopausal women, secondary hypogonadism was diagnosed by low estradiol in the presence of normal PRL and normal or low levels of gonadotrophins. In postmenopausal women, secondary hypogonadism was considered if serum gonadotrophins were low for age. Levels of IGF-I lower than reference values for age- and gender of control subjects were considered abnormal.

### **Statistical analysis**

Descriptive statistics are presented as mean value  $\pm$  SE. Statistical analysis was performed using the non-parametric Mann-Whitney test. The influence of age, BMI and GOS were analyzed with the Mann-Whitney test, while sex, localization of aneurysm, presence of cerebral vasospasm and/or hydrocephalus, epilepsy, arterial hypertension, diabetes mellitus and/or smoking habits were analyzed with the Chi-square test. Correlation between hormonal levels and various parameters in patients was analyzed using Spearman's correlation coefficient. The multiple logistic regression analysis with the Backward method was used to adjust for possible confounders on hormonal results. Analyses were performed using SPSS software (SPSS for Windows, release 10.0). P values less than 0.05 were regarded as indicating statistical significance.

## **RESULTS**

### **Study population**

Ninety-three SAH patients who fulfilled the inclusion and exclusion criteria were enrolled in the study. Subjects included 30 males and 63 females (23 premenopausal and 40 postmenopausal), aged  $48.0 \pm 1.1$  years, with a mean BMI of  $24.7 \pm 0.5$  kg/m<sup>2</sup> and a mean GOS score of  $4.6 \pm 0.6$ . In our population with SAH, more women (especially postmenopausal) than men were affected ( $p < 0.001$ ).

The patients were examined at least one year after the SAH (mean  $\pm$  SE:  $1.8 \pm 0.2$  years). The age at occurrence of SAH was (mean  $\pm$  SE)  $46.2 \pm 1.1$  years.

The location of the aneurysm was at the internal carotid artery (ICA) in 32 (34.4%), at the middle cerebral artery (MCA) in 30 (32.3%), at the anterior communicating artery (ACoA) in 22 (23.7%) and at the vertebrobasilar arteries in 9 (9.7%) patients. Cerebral vasospasm (VS) during the acute phase of SAH was registered in 18 (19.4%) patients, most frequently in patients with aneurysm of the ICA (10 of 32 cases). Hydrocephalus (HDC) during the acute phase of SAH was registered in 9 (9.7%) patients, most frequently in postmenopausal women. Two patients had both complications, cerebral VS and HDC, during the acute phase of SAH. Epilepsy, as a chronic complication of SAH, was diagnosed in four patients.

Arterial hypertension at the time of hemorrhage was diagnosed in 49 (52.7%) patients, most frequently in postmenopausal women. Five patients were diabetic at the time of acute hemorrhage and 57 (61.3%) were active smokers.

### Results of hormonal evaluation

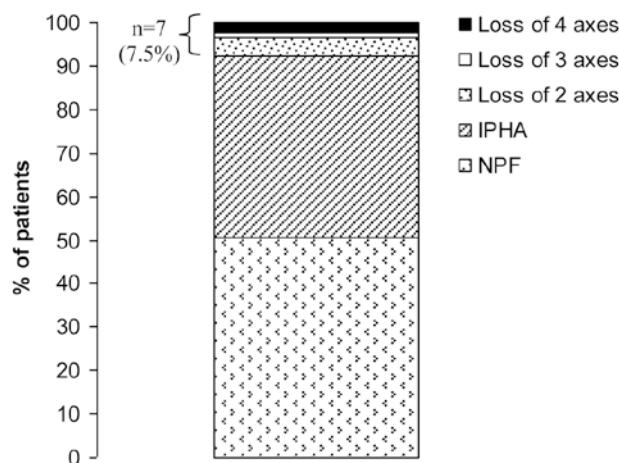
The prevalence of neuroendocrine dysfunction in SAH patients is presented in Figures 1 and 2. Overall, 47 patients (50.5%) had no abnormalities. Seven patients (7.5%) had multiple pituitary hormonal deficiencies (Figure 1): Four patients (4.3%) had dual abnormalities (GH and adrenal axis), one female patient had three abnormal axes (gonadal,

adrenal and GH) and two female patients had all four pituitary axes affected. Thirty-nine patients (42%) had a single abnormal axis (13 adrenal, 2 thyroid, 4 gonadal and 20 GH; Figure 2). None of the subjects had been treated with desmopressin or exhibited symptomatic polyuria.

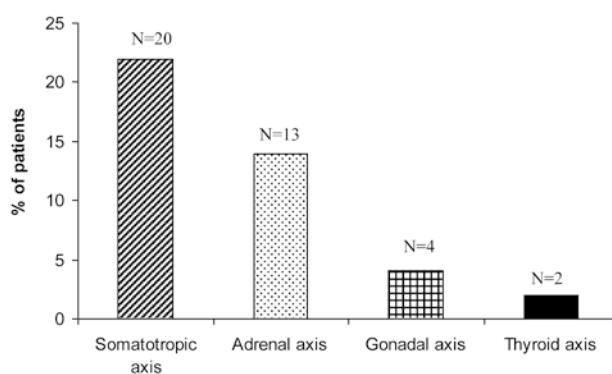
Clinical characteristics of patients with normal pituitary function (NPF), those with isolated pituitary hormone abnormality (IPHA) and those with multiple pituitary hormone abnormalities (MPHA) are presented in Table 1. Patients with MPHA and IPHA had increased incidence of cerebral VS compared with those with normal pituitary function ( $p<0.001$ ). Patients with IPHA had a lower GOS compared with patients with normal pituitary function ( $p=0.020$ ).

### Somatotrophic axis

IGF-I levels were below normal values for age- and sex-matched healthy subjects in 27 SAH patients (29.0%), indicating the need for GH provocative testing to confirm the diagnosis of GHD. In 20 patients GHD was an isolated pituitary hormone abnormality (IPHA; Figure 2), and in seven low IGF-I levels were combined with other pituitary hormone abnormali-



**Figure 1.** Prevalence of normal pituitary function (NPF; n=47, 50.5%), isolated pituitary hormone abnormality (IPHA; n=39, 42%) or loss of two, three and four pituitary axes (n=7, 7.5%) in patients tested more than one year after aneurysmal SAH.



**Figure 2.** Distribution of single pituitary deficit in 39 patients (42% of all SAH patients) tested more than one year after aneurysmal SAH.

**Table 1.** Clinical characteristics of patients with normal pituitary function (NPF), those with isolated pituitary hormone abnormality (IPHA) and those with multiple pituitary hormone abnormalities (MPHA)

	NPF	IPHA	MPHA
N	47	39	7
Sex (male/female)	17/30	11/28	2/5
Age (years)	49.3±1.4	45.5±1.7	54.8±1.7 <sup>d</sup>
BMI (kg/m <sup>2</sup> )	23.9±0.6	25.6±0.7 <sup>b</sup>	25.5±2.3 <sup>b</sup>
Time since SAH (yrs)	1.9±0.2	1.7±0.2	1.8±0.4
Vasospasm (yes/no)	2/45	13/26 <sup>a</sup>	3/4 <sup>a</sup>
Hydrocephalus (yes/no)	2/45	5/34	2/5
Epilepsy (yes/no)	4/43	0/39	0/7
GOS score	4.7±0.1	4.4±0.1 <sup>c</sup>	4.6±0.2
Hypertension (yes/no)	24/23	23/16	2/5
Diabetes mellitus (yes/no)	4/43	1/38	0/7
Smoking (yes/no)	29/18	25/14	3/4

<sup>a</sup>p <0.001 IPHA and MPHA vs. patients with NPF; <sup>b</sup>p <0.05 IPHA and MPHA vs. patients with NPF; <sup>c</sup>p <0.05 IPHA vs. patients with NPF; <sup>d</sup>p <0.05 MPHA vs. IPHA Descriptive statistics for continuous variables are presented as mean value ± SE.

ties. In four patients, low IGF-I level was associated with low morning cortisol levels (two axes affected). In one female, low IGF-I level was associated with low morning cortisol and estradiol/gonadotrophin levels (three axes affected), while in two females all four pituitary axes were affected.

The IGF-I level in patients with cerebral VS during the acute phase of SAH was significantly lower compared with patients without VS ( $74.3 \pm 18.5 \text{ ng/ml}$  vs.  $154.5 \pm 12.0 \text{ ng/ml}$ ;  $p < 0.001$ ; Figure 3a). The patients who had VS during the acute phase of SAH had 13.5-fold higher risk for low IGF-I level and possible GHD in the chronic phase ( $\text{OR} = 13.538$ ;  $p < 0.001$ ; 95% CI = 3.311–55.361; Table 2a). The IGF-I level was not significantly different in patients with and without HDC during the acute phase of SAH ( $p = 0.158$ ).

#### **Adrenal axis**

Basal morning cortisol levels were below the lower limit of normal range ( $< 131 \text{ nmol/l}$ ) in 20 of 93 patients (21.5%). In 13 patients, low cortisol levels presented as an isolated hormone deficiency (Figure 2). The remaining seven patients presented additionally low IGF-I levels (in four patients), low IGF-I and gonadotrophins deficiency (in one postmenopausal woman) and in two postmenopausal women low cortisol level was associated with impairment of all other pituitary axes.

The cortisol level in the patients with cerebral VS during the acute phase of SAH was significantly lower compared with patients without VS ( $230.6 \pm 25.4 \text{ nmol/l}$  vs.  $310.7 \pm 16.1 \text{ nmol/l}$ ;  $p < 0.05$ ; Figure 3a). The patients who had VS during the acute phase of SAH had 3.8-fold increased probability (not reaching statistical significance, defined by a  $p$  of less than 0.05, but still with a notable  $p$  of 0.073) of having low cortisol level and possible secondary hypocortisolism in the chronic phase ( $\text{OR} = 3.794$ ;  $p = 0.073$ ; 95% CI = 0.881–16.337). The presence of HDC during the acute phase of SAH increased the risk for low cortisol level more than 6-fold ( $\text{OR} = 6.346$ ;  $p = 0.012$ ; 95% CI = 1.499–26.867; Table 2b).

#### **Gonadal axis**

Total testosterone level was below the normal range in two (6.7%) of 30 males, presenting in both as an isolated hormone deficiency. There was no

correlation between testosterone levels and history of cerebral VS or HDC.

Of 63 female subjects, 40 (63.5%) were classified as postmenopausal by menstrual history. Of postmenopausal subjects high gonadotrophins were confirmed in 35, while five had inappropriately low gonadotrophins (secondary hypogonadism). In one patient secondary hypogonadism was combined with low basal cortisol and IGF-I levels, while in two postmenopausal women all pituitary axes were affected. A further 23 females had regular menstrual cycles.

#### **Thyroid axis**

T4 level was below the lower limit of the normal range in four of 93 patients (4.3%) and was associated with low-normal TSH levels (secondary hypothyroidism). In two patients secondary hypothyroidism was an IPHA, while in two all pituitary axes were affected.

#### **Lactotropic axis**

Prolactin levels were mildly elevated in four patients, combined in two cases with low IGF-I levels and in one female patient with impairment of all pituitary axes. There was no correlation between prolactin levels and history of cerebral VS or HDC.

#### ***Acute complications of SAH (cerebral vasospasm and hydrocephalus)***

Patients with cerebral VS had a lower GOS score compared with patients without cerebral VS during the acute phase of SAH ( $p < 0.001$ , Figure 3b). IGF-I and cortisol levels were significantly lower in patients with a history of VS compared with those without VS (Figure 3a). Two patients had both complications during the acute phase of SAH. One of them had three pituitary axes affected (low IGF-I, low cortisol and low gonadotropin levels), while the other patient had low cortisol levels.

#### ***Localization of aneurysm and endocrinological evaluation***

Results of hormonal analysis in patients divided into four groups according to the localization of aneurysm are presented in Table 3. Patients with aneurysm of ICA had a lower IGF-I level compared with patients with aneurysm of MCA ( $p < 0.05$ ). Male patients with aneurysm of VB had lower testosterone

**Table 2a.** The influence of confounding factors on IGF-I level (multiple logistic regression analysis with Backward method)

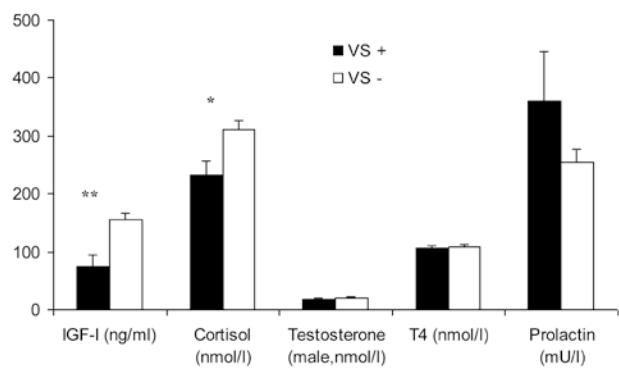
Logistic regression		95.0% CI for OR			
Method: Backward		p value	OR	Lower	Upper
First step	localization	0.958	1.016	0.552	1.871
	vasospasm	0.002	11.155	2.409	51.667
	hydrocephalus	0.338	2.511	0.382	16.489
	hypertension	0.947	0.961	0.293	3.145
	diabetes mellitus	0.580	0.457	0.028	7.343
	smoking	0.858	1.125	0.309	4.091
	epilepsy	0.999	0.000	0.000	.
	GOS score	0.493	0.714	0.273	1.868
	gender	0.651	1.371	0.349	5.382
Final step	vasospasm	0.000	13.538	3.311	55.361

OR – odd ratio; CI – confidence interval

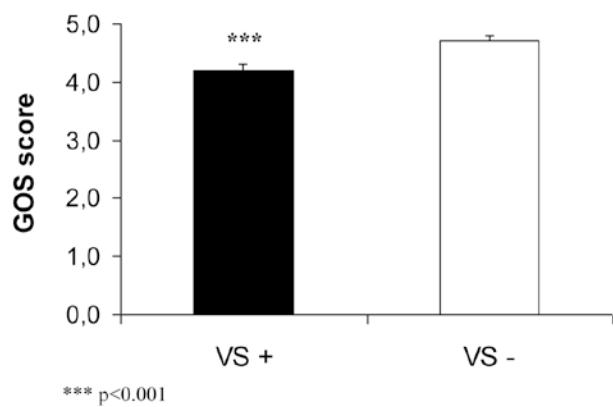
**Table 2b.** The influence of confounding factors on cortisol level (multiple logistic regression analysis with Backward method)

Logistic regression		95.0% CI for OR			
Method: Backward		p value	OR	Lower	Upper
First step	localization	0.472	0.784	0.403	1.522
	vasospasm	0.073	3.794	0.881	16.337
	hydrocephalus	0.010	9.021	1.688	48.219
	hypertension	0.505	1.513	0.447	5.117
	diabetes mellitus	0.185	0.445	0.134	1.474
	smoking	0.507	1.403	0.516	3.815
	epilepsy	0.298	0.487	0.126	1.884
	Final step	hydrocephalus	0.012	6.346	1.499

OR – odd ratio; CI – confidence interval

**FIGURE 3a.** Basal hormonal levels in patients with (VS+) and without vasospasm (VS-) during the acute phase of SAH.

level compared with patients with aneurysm of ICA ( $p <0.05$ ).

**FIGURE 3b.** Glasgow Outcome Scale (GOS) score in patients with (VS+) and without vasospasm (VS-) during the acute phase of SAH.

## DISCUSSION

The results of this study showed that almost half of the patients with SAH presented some degree of

**Table 3.** Hormonal analysis in patients with various localizations of the aneurysm

	<b>ICA</b>	<b>MCA</b>	<b>ACoA</b>	<b>VB</b>
N	32 (34.4%)	30 (32.3%)	22 (23.7%)	9 (9.7%)
T4 (nmol/l)	113.8 ± 4.5	106.1 ± 4.4	102.9 ± 5.9	106.2 ± 8.6
Testosterone (male, nmol/l)	21.0 ± 1.7	18.2 ± 5.2	19.6 ± 2.8	13.8 ± 0.9 b
Cortisol (nmol/l)	276.1 ± 20.7	303.5 ± 29.3	297.2 ± 28.5	331.9 ± 45.1
Prolactin (mU/l)	267.1 ± 23.6	247.6 ± 23.6	356.6 ± 68.5	202.6 ± 30.0
IGF-I (ng/ml)	109.5 ± 14.0a	162.9 ± 19.4	147.4 ± 28.7	126.2 ± 30.4

Descriptive statistics for continuous variables are presented as mean value ± SE

<sup>a</sup>p < 0.05 ICA vs MCA, <sup>b</sup>p < 0.05 ICA vs VB

ICA: Internal Carotid Artery, MCA: Middle Cerebral Artery, ACoA: Anterior Communicating Artery, VB: Vertebrobasilar Artery

hypopituitarism. Thirty-nine patients (42%) had one abnormal axis (20 GH, 13 adrenal, 4 gonadal and 2 thyroid) and seven (7.6%) had multiple abnormal axes. Of the seven patients with multiple abnormal axes, four had two abnormalities (GH and adrenal), one had three (GH, adrenal and gonadal) and two all four pituitary axes affected. The most vulnerable hypothalamic-pituitary axes were somatotropic and adrenal, while gonadal and thyroid axes were less frequently affected. Disturbances of the posterior pituitary were not encountered. Overall, half of the patients investigated one or more years after SAH presented with insufficiency of one or more anterior pituitary axes. The history of cerebral vasospasm and hydrocephalus during acute SAH was predictive for neuroendocrine dysfunction in the chronic phase.

Hypopituitarism may be the acute or chronic consequence of TBI and SAH.<sup>1-8,12</sup> The first large multicenter study on SAH patients was carried out by Aimaretti and colleagues who investigated 40 patients three months after SAH and diagnosed a variable degree of hypopituitarism in 37.5% of the patients.<sup>5</sup> In contrast to TBI, pituitary deficits after SAH are more often isolated than multiple and panhypopituitarism has not been reported. The most frequently affected pituitary axes in SAH survivors are the somatotropic axis and adrenal axis, as in our study.<sup>1-6</sup> Secondary hypogonadism was diagnosed in 13% of patients, while secondary hypothyroidism was less frequent, diagnosed in up to 7.5% of SAH survivors.<sup>5</sup> The diversity in the results of various studies following SAH may be attributed to differences in the methods used in the evaluation of neuroendocrine

function, particularly concerning the somatotropic and adrenal axes. In TBI and SAH patients the most frequently affected axis is the somatotropic.<sup>1-8</sup> Various tests have been used to diagnose GH deficiency, such as IGF-I determination and stimulatory tests (ITT and GHRH+arginine test).<sup>1-8</sup> The role of IGF-I in the diagnosis of adult GHD has been confusing due to the complexity of the regulation of IGF-I synthesis.<sup>23</sup> A considerable overlap exists in IGF-I levels between normal subjects and patients with GHD.<sup>24</sup> Serum IGF-I levels might be normal even in patients with total anterior hypopituitarism. However, despite the low diagnostic sensitivity of this parameter, very low levels of total IGF-I can be considered definitive evidence of severe GHD in a remarkable percentage of hypopituitary patients who could therefore skip provocative testing of GH secretion.<sup>25</sup> In our study, serum IGF-I measurements in adult patients investigated for possible GHD were compared with decade-based normative data and levels of IGF-I lower than the normative data were considered abnormal. Dimopoulos and colleagues found GHD in 37% of SAH patients based on low IGF-I level.<sup>3</sup> The most common alteration in their and our study was a diminished secretion of GH, as reflected by the finding of low IGF-I levels. We found IGF-I levels below decade-based normative data in 29% of SAH patients and identified the cerebral vasospasm during the acute phase of SAH as a risk factor for low IGF-I level in these patients. The studies in which a stimulatory test for GH was used revealed that 20-22% of SAH patients were GHD.<sup>2,4</sup> In our patients low IGF-I levels, particularly in those with IPHA,

underlines the need for GH provocative testing for confirmation of GHD.

The second most affected axis was the adrenal axis. Aimaretti and colleagues restricted the diagnosis of secondary hypocortisolism to the basal morning cortisol level less than 220 nmol/l and the low cortisol level in 24-hour urine.<sup>2,5</sup> In their study, secondary hypocortisolism was found in only 2.5% of SAH patients tested three months after the acute event. In another study, low-dose ACTH testing revealed secondary hypocortisolism in 10% of SAH patients tested 12-24 months after SAH.<sup>3</sup> In addition, when ITT was used, secondary hypocortisolism was diagnosed in 40% of SAH patients tested 12-72 months after SAH.<sup>4</sup> Schneider and colleagues reviewed the literature regarding SAH and pooled prevalences of hypopituitarism in the chronic phase of SAH. They found that 20.5% of SAH patients had secondary hypocortisolism.<sup>5</sup> These data are in accordance with our results. We identified 21.5% of SAH patients with low morning cortisol level. In published studies there is a high incidence of isolated corticotrophins deficiency following SAH.<sup>6</sup> These findings correspond to the neuropathological findings of selective hemorrhages into the paraventricular nuclei of the hypothalamus, indicating hypothalamic rather than pituitary dysfunction.<sup>26</sup> The findings of frequent hypocortisolism after SAH are in contrast to findings of neuroendocrine dysfunction following TBI in which LH/FSH and GH deficiencies are significantly more common than ACTH deficiency, which is also more common than TSH deficiency.<sup>6,8</sup>

Hypopituitarism is often associated with mild hyperprolactinemia resulting from neurosecretory dysfunction. In our study in three SAH patients hyperprolactinemia was associated with low IGF-I levels. Other deficits, e.g. gonadal and thyroid deficits, are less frequently observed in all published studies.

Systematic neuropathological investigations of the hypothalamo-pituitary axis after aneurysmal SAH have not been conducted so far. There are scarce pathological data about possible pathophysiological mechanisms of neuroendocrine dysfunction following SAH. Pathophysiological changes during the acute phase of SAH include the rise in intracranial pressure, cerebral vasospasm and impairment of

cerebral perfusion and focal or global brain edema. Furthermore, SAH can be complicated by intracerebral and intraventricular hemorrhage and acute hydrocephalus. Hemorrhage into the pituitary has frequently been observed after the rupture of an intracranial aneurysm.<sup>27</sup> Some authors described confluent hemorrhages which destroyed the pituitary gland and a hemorrhagic focus in the infundibulum in cases of increased intracranial pressure.<sup>28</sup> Neuropathological studies found evidences of morphological hypothalamic damage (hemorrhagic and ischemic changes) in 68% of patients who died shortly after the rupture of an intracranial aneurysm.<sup>26</sup> These microhemorrhages were selectively located in the paraventricular and supraoptic nuclei in most cases. The author postulated that this specific location of microhemorrhages was the consequence of the increased pressure in the chiasmatic cistern and a temporary obstruction of venous drainage in these nuclei. Ruptured aneurysms of the anterior communicating artery and the posterior communicating artery were more often associated with hypothalamic lesions than aneurysms of other locations. Thus, possible pathophysiological mechanisms of neuroendocrine dysfunction following SAH include: direct effect of hemorrhage, mechanical (an abrupt rise of intracranial pressure during the acute SAH), toxic, inflammatory and vascular (ischemia due to vasospasm).

The high percentage of disturbed somatotroph and adrenal axes in our study may represent an overestimation as the diagnosis is based on low basal cortisol and low IGF-I levels. We are aware that a number of patients with mild reduction of serum cortisol levels and IGF-I levels would respond normally to ITT, but this test is contraindicated in patients after recent brain injury.<sup>29</sup> It must be stressed, however, that adult GHD would be strongly predicted by very low IGF-I levels.<sup>23,26,30</sup>

In conclusion, neuroendocrine dysfunction following aneurysmal subarachnoid hemorrhage may occur at a much higher prevalence than previously suspected. High incidence of corticotroph and somatotroph dysfunction was observed in this study, with cerebral vasospasm and hydrocephalus emerging as the risk factors for dysfunction of the hypothalamo-pituitary axes.

There is a need for the formulation of an appropriate screening program for patients with brain injuries, which will help in the identification of subjects at high risk of developing an unrecognized hypopituitarism, a potentially serious but treatable complication of SAH. The presence of VS and HDC are factors that could be used for the selection of subjects with SAH who require further evaluation of pituitary function. Certainly, neurosurgeons, neurologists and endocrinologists should be aware of the considerable risk of pituitary dysfunction following SAH.

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