High Prevalence of Pituitary Dysfunction After Aneurysmal Subarachnoid Hemorrhage: A Long-Term Prospective Study Using Dynamic Endocrine Testing

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Key words
- Growth hormone deficiency
- Hypopituitarism
- Outcome
- Pituitary deficiency
- Subarachnoid hemorrhage

Abbreviations and Acronyms
ACTH: Adrenocorticotropic hormone
GH: Growth hormone
GHD: Growth hormone deficiency
GHRH: Growth hormone-releasing hormone
GOS: Glasgow outcome scale
HPA: Hypothalamic-pituitary-adrenal
IGF-1: Insulin-like growth factor 1
ITT: Insulin tolerance test
SAH: Subarachnoid hemorrhage
SST: Short Synacthen test

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OBJECTIVE: **Impaired systemic hormonal activity caused by hypothalamic and pituitary injury may contribute to neuropsychologic disturbances and poor quality of life after aneurysmal subarachnoid hemorrhage (SAH). This prospective study was designed to longitudinally evaluate long-term clinical outcome and pituitary function after SAH using dynamic tests for adrencorticotropic and somatotropic secretory capacity.**

METHODS: **Endocrine function was assessed by basal hormonal concentrations at 6–12 months and 12–24 months after SAH. At the 12–24 months follow-up, dynamic provocative evaluation of adrenocorticotropic hormone (ACTH) and growth hormone (GH) was performed using the insulin tolerance test (ITT). In patients where ITT was contraindicated, an ACTH stimulation test was used to assess ACTH capacity, and a growth hormone releasing hormone (GHRH)-arginine stimulation test was used to assess GH capacity.**

RESULTS: **Of 60 patients with SAH screened, 51 were included in the study, and 44 remained to be tested at the two follow-up visits. As assessed by basal hormone concentrations alone, the prevalence of pituitary dysfunction was 34% at 6–12 months and 41% at 12–24 months. When using dynamic tests (12–24 months), impaired pituitary function was detected in 43%. The ITT detected more cases of central hypoadrenalism and GH deficiency compared with the ACTH- and GHRH-arginine-stimulation tests, respectively.**

CONCLUSIONS: **Application of dynamic endocrine tests revealed a high frequency of long-term hypothalamic-pituitary dysfunction after aneurysmal SAH. The role of pituitary dysfunction in the recovery after SAH merits further evaluation.**

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (SAH) is associated with high mortality and significant neurological morbidity, often resulting in inability to return to independent living. During the past years more attention has been brought to the group of patients who have a good neurological outcome but still face long-lasting neuropsychologic disturbances (11). High prevalence of chronic fatigue and mood disorders persisting for several years after the bleed has been reported (20, 27). Mild cognitive deficits in patients with seemingly good recovery have been linked to impaired social functioning and well-being (23). Severe sleeping disturbances affecting many survivors of SAH may also be a potential cause for reduced quality of life (25). Structural hypothalamic and pituitary injury incurred in the acute phase by the SAH has been proposed as a contributing factor to such unsatisfactory recovery (3, 14, 24). Impaired systemic hormonal activity is a possible target for medical intervention. However, at present, clinical studies have reported remarkably diverse prevalence of pituitary insufficiency among patients with SAH, ranging from common (1, 6, 16) to nonexistent (15). Previous studies have mostly used adrenocorticotropic hormone (ACTH) and growth hormone-releasing hormone (GHRH)-arginine stimulation tests for these purposes. These tests have limitations. ACTH stimulation is an indirect way of evaluating central hypoadrenalism (9) and GHRH-arginine stimulation might miss suprapituitary defects (10).

The aim of the present study was to longitudinally evaluate endocrine function in a cohort of patients with aneurysmal SAH. Data on early outcome and endocrine profile have been presented previously (17). For a reliable assessment of the long-term effects on the hypothalamic-pituitary-adrenal (HPA) axis and growth hormone (GH) secretion, we used the insulin tolerance test (ITT), which is the gold standard for evaluation of hypothalamic-pituitary function. ACTH and GHRH-arginine stimulation tests were used only if induction of hypoglycemia was contraindicated.

METHODS

Patient Selection and Endocrine Evaluation

Patients with acute aneurysmal SAH admitted to the Department of Neurosurgery

at Skåne University Hospital in Lund were prospectively recruited for the study. The study protocol was approved by the Regional Ethical Review Board in Lund (65/2006) and registered at the ClinicalTrials.gov database (NCT01101711). Patients more than 18 years of age who could be subjected to hormonal blood sampling within 5–10 days after ictus were eligible for inclusion. Patients from whom informed consent could not be obtained and patients who declined to participate were excluded. Baseline characteristics and data on acute management have been described in detail earlier (17) and are summarized in **Table 1**. For the endocrine evaluation, blood and urine sampling was performed at 6–12 and 12–24 months after the bleed. For each patient at least 12 months elapsed between the 2 sampling occasions. Samples were collected in the morning (9 AM) for basal concentrations of plasma follicle-stimulating hormone, luteinizing hormone, estradiol (in women), testosterone (in men), sex hormone-binding globulin, thyroid-stimulating hormone, free thyroxin, ACTH, cortisol, prolactin, Na and K; serum levels of GH and insulin-like growth factor 1 (IGF-1); and serum and urine osmolality. Local reference values were used with addition of a graded interpretation of cortisol concentrations (5, 9) (**Table 2**). Gonadotropic function was assessed by estimations of basal concentrations of follicle-stimulating hormone and luteinizing hormone in relation to estradiol and premenopausal or postmenopausal state in women, or testosterone and sex hormone-binding globulin in men.

Assessment of endocrine function using dynamic tests was performed at 12–24 months. The ITT was used to evaluate somatotropic function and the HPA axis. A dose of 0.07 U/kg of short-acting insulin (Actrapid; Novo Nordisk, Bagsvaerd, Denmark) was administered intravenously. Blood samples for GH and cortisol analysis were drawn at 15 minutes before and at 0, 15, 30, 45, 60, 90, and 120 minutes after insulin administration. The tests were started at 9 AM with the patients fasting starting at midnight. Blood glucose concentrations were closely monitored. A decrease in blood glucose concentration to <2.2 mmol/L was considered a sufficient provocation (7). In response to this, peak GH concentrations of <3 μg/L indicate growth hormone deficiency (GHD) (10) and similarly, peak cortisol concentrations of <500 nmol/L indicate adrenocorticotropic deficiency (9). Patients were not subjected to ITT if they had a history of ischemic heart disease, epilepsy, or were older than 65 years of age. Patients with diabetes mellitus were also excluded from this test due to their unpredictable response to insulin. When the ITT was contraindicated, somatotropic function was assessed using the GHRH-arginine test and the HPA axis using the ACTH stimulation test. For the GHRH-arginine stimulation test, 1 μg/kg of GHRH and 500 mg/kg of arginine hydrochloride were administered intravenously. Concentrations of GH were subsequently measured after 15, 30, 45, 60, 75, and 90 minutes. GHD was defined as a peak GH response of <11 μg/L in patients with body mass index (BMI) of <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 (10). For the ACTH stimulation test, or short Synacthen test (SST), 0.25 mg of the ACTH analogue tetracosactrin (Synacthen, SOBI, Stockholm, Sweden) was injected intravenously. Samples for analysis of cortisol concentrations were collected 30 minutes before and 0, 30, and 60 minutes after administration. Peak cortisol concentrations <550 nmol/L were considered indicative of adrenocorticotropic dysfunction (9).

Table 1. Clinical Characteristics and Events Related to SAH (n = 51)

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, <1-mm thick	8 (16%)
3: Diffuse SAH, ≥1-mm 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 cm/s	17 (33%)
Angioplasty	6 (12%)

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.

Clinical Outcome Assessment

Clinical outcome was assessed by investigators E.K. or O.G.N. at the same follow-up visits as the endocrine evaluation and graded according to the Glasgow outcome scale (GOS) (12). The assessment was blinded to the results from the endocrine evaluation.

Statistical Analysis

All statistical analyses were made using SPSS version 22 (IBM Corporation, Armonk, New York, USA). The Mann-Whitney U test was used for comparisons of medians, and the Fisher's exact test was used for binary outcome parameters. Values of $P < 0.05$ were considered statistically significant.

RESULTS

Study Population and Clinical Outcome

Of 60 patients screened, 51 were included in the study, and 46 remained for the follow-up period presented here. With 2 patients (#19 and #20) unavailable within the set time frame, 44 were subjected to testing at 6–12 months. Two other patients (#13 and #16) withdrew their consent to participate before follow-up at 12–24 months, leaving 44 for the last evaluation (**Figure 1**).