Pituitary Dysfunction After Aneurysmal Subarachnoid Hemorrhage Is Associated with Impaired Early Outcome

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

Abbreviations and Acronyms
ACTH: Adrenocorticotropic hormone
BMI: Body mass index
CT: Computed tomography
FSH: Follicle-stimulating hormone
fT4: Free thyroxin
GH: Growth hormone
GHD: Growth hormone deficiency
GHRH: Growth hormone releasing hormone
GOS: Glasgow Outcome Scale
ICA: Internal carotid artery
IGF-1: Insulin-like growth factor 1
ITT: Insulin tolerance test
LH: Luteinizing hormone
MCA: Middle cerebral artery
SAH: Subarachnoid hemorrhage
SHBG: Sex hormone–binding globulin
TSH: Thyroid-stimulating hormone

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OBJECTIVE: **Poor outcome and neuropsychological sequelae after aneurysmal subarachnoid hemorrhage (SAH) is a persistent 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 to 10 days and 3 to 6 months after SAH. Growth hormone deficiency also was evaluated by the growth hormone releasing hormone–arginine stimulation test at follow-up. Clinical outcome was assessed and scored according to the Glasgow Outcome Scale.**

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 Glasgow Outcome Scale 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 is 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 neurointensive care (8), new technical strategies in treating ruptured aneurysms (5), and advances in monitoring and managing complications such as vasospasm and delayed cerebral ischemia (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 in patients with good neurological recovery (21, 34, 36). This has prompted further investigations of possible factors affecting the clinical course after 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 an impact on outcome after SAH (6). Indeed, some studies have reported endocrine abnormalities indicating pituitary dysfunction after 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 after traumatic brain injury (29). Neuropsychological and cognitive deficits have been described previously 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 this study was to investigate the prevalence of pituitary dysfunction in patients with aneurysmal SAH. The patients were 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 related to clinical features, including extent of hemorrhage seen on

computed tomography (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). Because earlier studies had included 30 to 40 patients with a 37.5% to 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 neurointensive 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 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 to 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 μmol/L) (27) was treated. The cause of hyponatremia after SAH is usually attributed to either cerebral salt wasting or syndrome of inappropriate antidiuretic hormone secretion (15). Neurological status was closely monitored 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 1 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 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 follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (in women), testosterone (in men), sex hormone–binding globulin (SHBG), thyroid-stimulating hormone (TSH), free thyroxin (fT4), adrenocorticotropic hormone (ACTH), cortisol, prolactin, Na, K; serum levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1); and serum and urine osmolality. Samples were drawn on day 5 to 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 growth hormone releasing hormone (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. GHD 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 to 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, cutoff levels were set at 100, 250, and 450 nmol/L. These levels were chosen because 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 to 22 IE/L for premenopausal women, 25 to 135 IE/L for postmenopausal women, 1.5 to 13 IE/L for men; LH: 1.0 to 96 IE/L for premenopausal women, 7.7 to 59 IE/L for postmenopausal women, 1.7 to 8.6 IE/L for men; estradiol: 90 to 1500 pmol/L for premenopausal women, <150 pmol/L for postmenopausal women; testosterone: 7.6 to 31 nmol/L for men <50 years, 4.6 to 31 nmol/L for men >50 years; SHBG: 14 to 48 nmol/L; TSH: 0.40 to 4.0 mIE/L; fT4: 12 to 22 pmol/L; ACTH: 1.0 to 13 pmol/L; prolactin: 3 to 22 μg/L; Na: 136 to 146 mmol/L; K: 3.2 to 4.7 mmol/L; IGF-1: 116 to 358 μg/L for ages 21 to 25 years, 117 to 329 μg/L for ages 26 to 30 years, 115 to 307 μg/L for ages 31 to 35 years, 109 to 284 μg/L for ages 36 to 40 years, 101 to 267 μg/L for ages 41 to 45 years, 94 to 252 μg/L for ages 46 to 50 years, 87 to 238 μg/L for ages 51 to 55 years, 81 to 225 μg/L for ages 56 to 60 years, 75 to 212 μg/L for ages 61 to 65 years, 69 to 200 μg/L for ages 66 to 70 years, 64 to 188 μg/L for ages 71 to 75 years, 59 to 177 μg/L for ages 76 to 80 years; and serum osmolality: 280 to 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 to 6 months later in the outpatient clinic according to study protocol. The evaluation was performed blinded to the endocrine data by 2 investigators (E.K. or O.G.N.).