CLINICS

CLINICAL SCIENCE

Pituitary deficiency after aneurysmal subarachnoid hemorrhage

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OBJECTIVE: Aneurysmal subarachnoid hemorrhage puts patients at high risk for the development of pituitary insufficiency. We evaluated the incidence of pituitary dysfunction in these patients and its correlation with clinical outcome.

METHODS: Pituitary function was tested in 66 consecutive patients in the first 15 days after aneurysmal subarachnoid hemorrhage. The following were measured in all patients: thyroid-stimulating hormone, free thyroxine, triiodothyronine, luteinizing hormone, follicle-stimulating hormone, total testosterone (in males), estradiol (in females), prolactin, serum cortisol, plasma adrenocorticotropic hormone, growth hormone and insulin growth factor.

RESULTS: The endocrine assessment was made at a mean of 7.4 days (standard deviation $\pm$6.6) after subarachnoid hemorrhage. Forty-four (66.7%) female and 22 (33.3%) male patients were evaluated. Thirty-nine patients (59.1%) had some type of pituitary dysfunction. Follicle-stimulating hormone/luteinizing hormone deficiency was the most frequent disorder (34.8%), followed by growth hormone/insulin growth factor (28.7%), adrenocorticotropic hormone (18.1%) and thyroid-stimulating hormone (9%). Seventeen (25.7%) patients showed deficiencies in more than one axis. A greater incidence of hormone deficiency was observed in patients with a Glasgow Coma Scale score $\leq$13 (t test, $p = 0.008$), Hunt-Hess grade $\geq$4 (t test, $p<0.001$), or Fisher grade 4 (t test, $p = 0.039$). Hormone deficiency was not significantly associated ($p>0.05$) with increased hospitalization or clinical outcome.

CONCLUSION: Pituitary dysfunction was identified in a substantial portion of patients with previous aneurysmal subarachnoid hemorrhage, but no association was found between this dysfunction and poor clinical outcome.

KEYWORDS: Subarachnoid Hemorrhage; Endocrine Dysfunction; Aneurysm.

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INTRODUCTION

Spontaneous subarachnoid hemorrhage (SAH) is a disease with high morbimortality that affects the economically active population. Its six-month mortality rate ranges from 40 to 50%. In recent years, research has focused on factors related to diminished quality of life in patients with SAH and with good neurological recovery (*1,2*). One of these factors is neuroendocrine dysfunction following SAH. Nonspecific symptoms that occur frequently and can provoke important limitations include fatigue, headaches, mood swings, depression, cognitive impairment and reduced independence in daily activities, which may be related to hypopituitarism (3-6).

Some evidence of the relationship between pituitary dysfunction and SAH has been reported in the literature. A number of studies have suggested that endocrine disorders are caused by compression of the hypothalamus-pituitary complex by the aneurysm. Other reported causes are the SAH itself due to perfusion alterations, toxins from extravasated blood, ischemia due to vasospasm, increased intracranial pressure, and hydrocephalus. One additional cause is injury during the surgical procedure (6-9).

Determining the incidence and prevalence of hypopituitarism in patients with SAH is fundamental because this would permit the study of more effective measures to improve the quality of life of patients with this serious disease (4,6,10,11). The main objective of this study was to evaluate the incidence of hypopituitarism in the first 15 days after SAH to assess its implications for prognosis and hospitalization period.

No potential conflict of interest was reported.

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MATERIALS AND METHODS

Patients

This study evaluated 66 patients admitted to the Neurosurgical Service of Santa Casa Hospital at Belo Horizonte between December 2009 and December 2010 with a diagnosis of SAH secondary to cerebral aneurysm rupture, which was confirmed by CT scan and digital subtraction cerebral angiography (DSA) of the four vessels.

Clinical evaluation was performed at admission using the Glasgow Coma Scale (GCS). SAH severity was graded clinically using the Hunt-Hess scale (HH) and radiologically using the Fisher scale. The presence of hydrocephalus was recorded at the time of discharge. Clinical outcome was evaluated by the Glasgow Outcome Scale (GOS) at hospital discharge by one of the authors; a score of 4 or 5 was considered a favorable outcome, and 1 to 3 was considered a poor outcome.

The inclusion criteria were SAH secondary to ruptured aneurysm, an absence of endocrine changes prior to hormone data collection (performed within the first 15 days after SAH) and patient age ≥18 years. The exclusion criteria were patients younger than 18 years, more than 15 days since the ictus of SAH, those with prior endocrine dysfunction, those who refused endocrine tests, patients whose data were not collected properly and those who had recent or prolonged use of corticosteroids. Out of the 93 patients initially assessed, 27 were excluded: 1 due to age, 3 for prior endocrine dysfunction, 5 for previous use of corticosteroids (steroid administration is still a common practice in many units) and 18 due to a lack of complete hormone data (some patients required urgent surgery; therefore, complete endocrine assessment was impossible) or evaluation more than 15 days after SAH. The resulting study population consisted of 66 patients. None of these patients presented severe liver disease, coronary heart disease, kidney disease, severe depression or uncontrolled diabetes mellitus.

Endocrine function testing

Blood samples for hormonal assessment were collected on the first morning after admission after the patient had fasted for at least 8 hours, when this practice would not compromise the surgical decision. The endocrine assessment was performed at a mean of 7.4 days (SD±6.6) after ictus. Posterior pituitary deficiency was not evaluated.

We used commercially available kits to determine hormone levels. Morning cortisol, morning adrenocorticotropic hormone (ACTH), growth hormone (GH), insulin growth factor (IGF-1), thyroid-stimulating hormone (TSH), free thyroxine (fT4), total triiodothyronine (T3), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (for women), testosterone (for men) and prolactin were measured using chemiluminescence or immunoassay methods. The reference values were appropriate for patient age and sex in accordance with the manufacturer's recommendations. The hormonal levels obtained, together with the respective methods and reference values, are presented in Table 1.

The following criteria were used to diagnose hormonal disturbances:

- ACTH deficiency was diagnosed based on low cortisol associated with low or inappropriately normal ACTH.
- GH deficiency was diagnosed based on low IGF-1.
- TSH deficiency was defined as decreased fT4 in the presence of inadequately low basal TSH.
- Prolactin disturbance was diagnosed based on high prolactin.
- Gonadotropin deficiency was diagnosed based on basal LH and FSH levels, testosterone levels in men, and estradiol levels and the presence of menstrual disturbances in women.

Because there is no consensus regarding endocrine assessment and treatment after SAH, hormone reposition therapy was not performed in our series.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences Base Version 9.0 for Windows, SPSS Inc. 1998, Chicago, IL). Mann-Whitney U tests were performed for rank-ordered variables, chi-square tests for categorical variables, and t tests for variables counted on an interval scale. Bivariate correlations were calculated with Pearson correlation coefficients.

Ethics

This study was performed in accordance with the ethical standards of the responsible committee on human experimentation of Santa Casa de Belo Horizonte and the Helsinki Declaration of 1975 (1983 revision). Written informed consent was obtained from the patients or someone responsible for them.

RESULTS

Sixty-six patients were evaluated; 44 (66.7%) were female. The mean patient age was 48.3±13.8 years (25-83 years). Admission data, including the Hunt-Hess scale, Fisher grade and neurological outcome, are presented in Table 2. Fifty-four out of the 66 patients (81.8%) were submitted to microsurgical clipping, and the remainder underwent endovascular occlusion of the aneurysm. The mortality rate was 15.1% (n=10). Twenty-five (37.8%) patients had an adverse outcome (GOS 1-3).

Endocrinological disorders

The endocrine assessment was made at a mean of 7.4 days following SAH. The incidence of some degree of hypopituitarism after aneurysmal SAH was 59.0% (39 patients). FSH/LH deficiency was the most frequent disorder (34.8%), followed by GH/IGF-1 (28.7%), ACTH (18.1%), and TSH (9%). Five (9%) patients presented high prolactin. Seventeen (25.7%) patients showed disturbances in more than one axis. The profile of pure hormone disturbances and multiple hormone disturbances is detailed in Table 3.

Corticotrophic axis

Cortisol levels below 4 μg/dl associated with low or inappropriately normal ACTH, which was compatible with secondary adrenal deficiency, was detected in 8 patients (12.1%), 5 (62.5%) of whom were female. The mean age of these patients was 42.7±8.4 years (25-52 years). The mortality rate was 25.0% (n=2). Patient evolution was favorable in 5 (64.5%) cases and poor in 3 (37.5%).

Somatotrophic axis

Low IGF-1 levels were detected in 19 (28.7%) patients, of whom 16 (84.2%) were female. Their mean age was 51.4±13.2 years (27-77 years), and their mortality rate was

Table 1 - Hormonal evaluations, with their respective methods and reference values.

Hormone	Method	Reference value	Kit
Cortisol (morning)	Chemiluminescence	4.3 to 22.4 μg/dL	Beckman Coulter®
ACTH (morning)	Chemiluminescence	0 to 46 pg/mL	Siemens®
GH	Chemiluminescence	0 to 0.5 ng/mL	Siemens®
IGF-1	Chemiluminescence	91 to 246 ng/mL	Siemens®
TSH	Chemiluminescence	0.35 to 5.5 mcUI/mL	Beckman Coulter®
Free T4	Chemiluminescence	0.7 to 2.0 ng/dL	Beckman Coulter®
T3	Chemiluminescence	0.6 to 1.81 ng/mL	Beckman Coulter®
FSH	Chemiluminescence	Women: Follicular phase: 2.5 to 10.2 μIU/mL Mid-cycle: 3.4 to 33.4 μIU/mL Luteal phase: 1.5 to 9.1 μIU/mL Postmenopause: 23.0 to 116.3 μIU/mL Men: 1.4 to 18.1 μIU/mL	Beckman Coulter®
LH	Chemiluminescence	Women: Follicular phase: 1.9 to 12.5 mIU/mL Mid-cycle: 8.7 to 76.3 mIU/mL Luteal phase: 0.5 to 16.9 mIU/mL Postmenopause: 15.9 to 54.0 mIU/mL Men: Aged 20 to 70 years: 1.5 to 9.3 mIU/mL Over 70 years: 3.1 to 34.6 mIU/mL)	Beckman Coulter®
Prolactin	Chemiluminescence	Women: Nonpregnant: 2.8 to 29.2 ng/mL Pregnant: 9.7 to 208.5 ng/mL Postmenopause: 1.8 to 20.3 ng/mL; Men: 2.1 to 17.7 ng/mL	Beckman Coulter®
Total testosterone	Immunoassay	Men (18 to 60 years): 241 to 827 ng/dL	Beckman Coulter®
Free testosterone	Immunoassay	Men (18 to 60 years): 6.2 to 28.1 pg/mL	Beckman Coulter®
Estradiol	Chemiluminescence	Women: Follicular phase: 18.9 to 246.7 pg/mL Mid-cycle: 35.5 to 570.8 pg/mL Luteal phase: 22.4 to 256 pg/mL Postmenopause: <30 pg/mL	Beckman Coulter®

ACTH, adrenocorticotropic hormone; GH, growth hormone; IGF-1, insulin growth factor; TSH, thyroid-stimulating hormone; fT4, free thyroxine; T3, total triiodothyronine; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

26.3% (n = 5). Clinical evolution was favorable in 12 (63.2%) patients and poor in 7 (36.8%).

Thyroid-stimulating hormone (TSH)–free T4 axis

Low TSH was detected in 6 (9.0%) patients, 4 (66.7%) of whom were female. Their mean age was 41.3 ± 3.8 years (36-47 years). None of the patients with low TSH presented low free T4 or T3. One patient with low TSH presented high free T4. The mortality rate in the group with low TSH was 16.7% (n = 1). Clinical evolution was favorable in 3 (50%) patients and poor in 3 (50%).

Prolactin

High prolactin was detected in 6 (9%) patients, 5 (83.3%) of whom were female. Its incidence was 4.5% in men and 11.3% in women. The mean age of this group was 49.8 ± 4.5 years (45-58 years), and the mortality rate was 0% (n = 0). Clinical evolution was favorable in 4 (66.7%) patients and poor in 2 (33.3%).

Gonadotropic axis

Low FSH/LH was detected in 23 (34.8%) patients, 14 (60.8%) of whom were female. Their mean age was 47.8 ± 15.4 years (25-83 years). Their mortality rate was 26.1% (n = 6). Clinical evolution was favorable in 14 (60.9%) patients and poor in 9 (39.1%).

Among men, low testosterone levels were detected in 13 (59.1%) patients. The mean age of men with low testosterone was 46.3 ± 10.5 years (25-61 years), and their mortality rate was 30.8% (n = 4). Clinical evolution was favorable in 7 (53.8%) patients and poor in 6 (46.2%).

Among women, low estradiol was detected in 13 (29.5%) patients. The mean age of women with low estradiol was 50.6 ± 16.9 years (26-83 years), and their mortality rate was 23.1% (n = 3). Clinical evolution was favorable in 7 (53.8%) patients and poor in 6 (46.2%).

Endocrinological disorders *versus* clinical assessment and outcome

A greater incidence of hormone deficiency was observed in patients with GCS ≤13 (t test, $p = 0.008$), in patients with a Hunt-Hess grade ≥4 (t test, $p < 0.001$), and in patients with a Fisher grade of 4 (t test, $p = 0.039$).

Hormone deficiency was not significantly associated ($p > 0.05$) with a longer hospitalization period. Poor outcome (GOS 1-3) was observed in 41.0% (n = 16) of the patients with hormonal deficiency compared with 33.3% (n = 9) in the group with no hormonal change ($p > 0.05$).

No statistically significant difference was verified ($p > 0.05$) in the hospitalization period or outcome in the hormonal subgroups (Table 3).

DISCUSSION

The pathophysiology of neuroendocrine dysfunction following aneurysmal subarachnoid hemorrhage remains

Table 2 - Demographic and clinical data of the study population.

--	General	With dysfunction	Without dysfunction	*p*-value
N	66 (100%)	39 (59%)	27 (41%)	
Age, years	48.3±13.8	47.9±13.4	49.0±14.7	>0.05
Sex				>0.05
Male	22 (33.3%)	14 (35.8%)	8 (29.6%)	
Female	44 (66.6%)	25 (64.1%)	19 (70.3%)	
Hospitalization duration, days	19.9±19.1	20.6±13.4	18.9±25.2	>0.05
Treatment modality				
Clipping	54 (81.8%)	31 (79.4%)	23 (85.1%)	>0.05
Coils	12 (18.1%)	8 (20.5%)	4 (14.9%)	
Hydrocephalus	7 (10.6%)	5 (12.8%)	2 (7.4%)	>0.05
GCS	13.8±2.5	13.2±3.1	14.7±0.6	0.008 ECG≤13
Hunt-Hess				
I	32 (48.4%)	16 (41.0%)	16 (59.2%)	<0.001
II	15 (22.7%)	10 (25.6%)	5 (18.5%)	HH≥4
III	13 (19.6%)	9 (23.0%)	4 (14.8%)	
IV	4 (6.0%)	2 (5.1%)	2 (7.4%)	
V	2 (3.0%)	2 (5.1%)	0 (0%)	
Fisher				
I	7 (10.6%)	3 (7.6%)	4 (14.8%)	0.039
II	14 (21.2%)	8 (20.5%)	6 (22.2%)	Fisher≥4
III	33 (50.0%)	18 (46.1%)	15 (55.5%)	
IV	12 (18.1%)	10 (25.6%)	2 (7.4%)	
GOS				
1-3	25 (37.8%)	16 (41.0%)	9 (33.3%)	>0.05
4-5	41 (62.1%)	23 (59.0%)	18 (66.6%)	
Mortality	10 (15.1%)	8 (20.5%)	2 (7.4%)	>0.05

N: number; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale.

unknown. Some studies have suggested that ischemic or hemorrhagic lesions in the hypothalamus or pituitary gland may be the genesis of such changes (6).

The incidence and prevalence of neuroendocrine dysfunction have been the focus of research on some neurological diseases, such as SAH and traumatic brain injury (TBI), and, to a lesser extent, in radiation therapy on the central nervous system, ischemic stroke and neurosurgical procedures for non-pituitary tumors (7,8,12-16).

Previous studies have investigated pituitary dysfunctions in the late period of the first days and the first hours after SAH. The present study analyzed the first 15-day period and detected a high incidence of hypopituitarism (59% of the cases). We observed that FSH/LH deficiency was the most prevalent disorder (34.8%), followed by GH/IGF-1 (28.7%), ACTH (18.1%) and TSH (9%). Seventeen (25.7%) patients showed deficiencies in more than one axis. Our results are similar to Klose et al. (17), who analyzed hormonal changes in 26 patients at a mean of 7 days following SAH and detected an incidence of pituitary alterations of 58%. Klose et al. (17) detected low FSH/LH in 93.3% of patients, low T3 in 35%, low cortisol in 12% and low GH/IGF-1 in 15%.

Table 3 - Incidence of hormone disturbances indicating anterior pituitary dysfunction in patients with SAH.

Hormone disturbance	n	%
Isolated gonadotrophic	10	15.1
Isolated somatotrophic	9	13.6
Isolated corticotrophic	1	1.5
Prolactin	0	0.0
Isolated thyrotrophic	0	0.0
Somatotrophic + gonadotrophic	4	6.0
Somatotrophic + prolactin	3	4.5
Corticotrophic + gonadotrophic + thyrotrophic	3	4.5
Gonadotrophic + prolactin	3	4.5
Corticotrophic + gonadotrophic	2	3.0
Somatotrophic + thyrotrophic	1	1.5
Corticotrophic + thyrotrophic	1	1.5
Corticotrophic + somatotrophic + gonadotrophic	1	1.5
Total	39	59.0

In our analysis, patients who presented a more severe clinical status on the HH and GCS evaluations and greater bleeding on tomography (Fisher grade) showed a higher propensity for endocrinological disorders. Klose et al. (17) observed a correlation between lower GCS and the presence of hydrocephalus with hormonal changes in the first days after SAH. Schneider et al. (6) did not find a statistically significant relationship between HH or Fisher grade and endocrinological disorders in the late period after SAH. We did not find a relationship between the presence of hydrocephalus and endocrine changes. We also did not find a correlation between the incidence of neuroendocrine dysfunction and clinical outcome. This finding may be explained at least in part by the selection bias. Our service is a reference center, and most patients are admitted after the first days of SAH. Our endocrinological assessment was performed at a mean of 7.4 days, which favored the inclusion of patients with a good neurological outcome and most likely a better clinical state on admission. Furthermore, the limited number of patients combined with the significant amount of stratification (generating even small subgroups of hormone deficiency) may have resulted in a reduced power of the statistical analyses.

Mangieri et al. (18) studied the hormonal profiles of patients in the hyperacute phase of SAH (the first 24 hours). They observed an increase in cortisol in all patients studied (n = 35), most likely due to the physiological response to

stress. They also observed a greater incidence of high prolactin (14.2%). Regarding thyroid hormones, they observed high TSH in 14.2% of patients, low T3 in 14.2% and low T4 in 5.6%, whereas FSH and LH were unaffected.

In a review by Schneider et al. (6) regarding hormonal dysfunction in SAH, they identified 5 papers on pituitary dysfunction in late-stage SAH (6 months following ictus) that included 102 patients. This review found a mean prevalence of hormonal dysfunction of 47% (37.5-55%) (3-8,14). Schneider et al. (6) also observed large differences in the frequency of the different anterior pituitary axes affected: GH (25.4%) and ACTH (20.5%) deficiencies were the most common, followed by FSH/LH (5.9%) and TSH (5.9%) deficiencies. Multiple deficiencies were detected in 8.8% of patients. In contrast, Klose et al. (17) evaluated 62 patients at a mean of 14 months after ictus and detected a post-SAH prevalence of hormonal dysfunction of 13%. To improve the lack of knowledge that exists today on endocrine deficiency following SAH, we are still following up with this series of patients. Our aims are to evaluate their later pituitary function to corroborate not only the incidence but also the prevalence of this disorder as well as to correlate pituitary dysfunction with delayed functional state.

We believe that our study found a higher rate of hormonal dysfunction (incidence) than papers analyzing the late phase after SAH (prevalence) because most pituitary dysfunctions are transient; i.e., hormonal dysfunction is greater when examined in the first days after SAH and decreases over time. An analogous situation has been observed in hormonal evaluations in traumatic brain injury (TBI) patients, in which a trend toward improvement in hormonal dysfunctions occurs in some patients over a year-long assessment (6,19). Aimaretti et al. (8) observed a reduction in the prevalence of hormonal dysfunction following SAH from 47% at three months to 38% at 12 months.

It is important to note that some pituitary functions are better evaluated using a combined TRH-LHRH-arginine (ARG) test and an insulin tolerance test (ITT) instead of basal measures. Some authors have used those tests in patients with SAH between 12 and 72 months after the ictus (5), but it is difficult and dangerous to perform those tests in the acute phase. Thus, those tests were not performed in our group.

In this paper, we did not evaluate posterior pituitary deficiency, which is primarily represented by sodium imbalance secondary to antidiuretic hormone (ADH) dysfunction, because this dysfunction is already a well-known condition in patients with SAH and patients submitted to neurosurgery approaches.

In the present study, hormonal evaluation in the first two weeks after SAH revealed a high incidence of pituitary dysfunction that was not related to prognosis or hospitalization period.

AUTHOR CONTRIBUTIONS

Pereira JL and Albuquerque LA contributed to the manuscript writing and literature review. Dellaretti M, Carvalho GT and Sousa AA reviewed the manuscript. Vieira Jr G wrote the manuscript. Brochado VM, Drummond AV, Morais JE and Ferreira LM collected the data. Miranda PA performed the endocrinologic analysis.

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