Pituitary Hormonal Disturbances in Aneurysmal Subarachnoid Hemorrhage

Distúrbios hormonais pituitários na hemorragia subaracnóidea aneurismática

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Abstract

Objective The objective of the present study was to assess the hormonal alterations that occurred in patients with subarachnoid hemorrhage.

Methods This is a case series with 21 patients diagnosed with subarachnoid hemorrhage of aneurysmal etiology up to 30 days after the ictus. The following hormonal measurements were performed in these patients: cortisol, GH, testosterone, prolactin, estradiol, FSH, LH, FSH, T3, T4 and free T4. The hormonal results of the cases were compared with the results of twelve volunteers from the control group and correlated with findings in brain tomography, cerebral angiography, Hunt-Hess scale, and vasospasm.

Results The main altered hormones were cortisol (52.6%), GH (42.9%) and TSH (28.6%). There was a trend towards more severe cases in the following groups of patients: Hunt-Hess scale > 2, Fisher scale > 1, aneurysmal topography in the anterior communicating artery and those who had vasospasm.

Conclusion The present study observed the tendency of pituitary hormonal changes in patients with subarachnoid hemorrhage of aneurysmal etiology, corroborating the need for dosage of hormones from the hypothalamic-pituitary axis in the management of these cases.

Keywords
- pituitary gland
- pan-hypopituitarism
- subarachnoid hemorrhage
- hormone abnormalities
- intracranial aneurysm

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Resumo

Objetivo O objetivo do presente estudo foi avaliar as alterações hormonais em pacientes com hemorragia subaracnóidea e correlacionar tais alterações com a gravidade da hemorragia.

Métodos Trata-se de uma série de casos com 21 pacientes com diagnóstico de hemorragia subaracnóidea de etiologia aneurismática até 30 dias do ictus. Foram realizadas as seguintes dosagens hormonais nesses pacientes: cortisol, GH, testosterona, prolactina, estradiol, FSH, LH, FSH, T3, T4 e T4 livre. Os resultados hormonais dos casos foram comparados com os resultados de 12 voluntários do grupo controle e correlacionados com achados em tomografia de crânio, estudo angiográfico cerebral, escala de Hunt-Hess e vasoespasmo.

Resultados Os principais hormônios alterados foram o cortisol (52,6%), GH (42,9%) e o TSH (28,6%). Houve uma tendência de casos mais graves nos seguintes grupos de pacientes: escala de Hunt-Hess > 2, escala de Fisher > 1, topografia aneurismática na artéria comunicante anterior e aqueles que cursaram com o vasoespasmo.

Conclusão O presente estudo observou a tendência de alterações hormonais hipofisárias em pacientes com hemorragia subaracnóidea de etiologia aneurismática, corroborando a necessidade de dosagem dos hormônios do eixo hipotálamo-hipofisário no manejo desses casos.

Palavras-chave

- hipófise
- pan-hipopituitarismo
- hemorragia subaracnóidea
- anormalidades hormonais
- aneurisma intracraniano

Introduction

Hormonal changes associated with hypothalamic-pituitary dysfunction may occur during subarachnoid hemorrhage or as a result of mass effect on the hypothalamus-pituitary exerted by cerebral aneurysms.[1,2]

The first description of pituitary dysfunction associated with the presence of an intracranial aneurysm was reported in 1887 by Bramwell.[3] This author reported the case of a man with 31 years and a history of cognitive disorder, habit, decreased vision, decreased head and pubic hair, testicular atrophy, and gynecomastia. At the time of autopsy, an aneurysm of the internal carotid artery was diagnosed, related to the sella turcica and its content, that is, the pituitary gland.[3]

Horn brook and Marks, in 1961, studied three women with hypopituitarism associated with intracranial aneurysm, and raised the hypothesis that pituitary dysfunction is a consequence of the interference of the aneurysm with the blood supply of the hypothalamic nuclei.[4] All the patients improved with hormone replacement.

We stress that even though historical records suggest a possible hormonal dysfunction with the presence of intracranial aneurysms, there are few studies evaluating pituitary function after aneurysmal subarachnoid hemorrhage (SAH).

The present study aimed to assess possible hormonal changes in patients who suffered intracranial aneurysm rupture.

Methods

We conducted a prospective study involving 21 patients diagnosed with SAH by rupturing an intracranial aneurysm in the Hospital da Restauração, Recife, state of Pernambuco, Brazil. One hundred and thirty-five blood collections were made, and in 5 patients, the blood samples were made in the pre- and postoperative periods, totaling 1,350 hormonal dosages.

The inclusion criterion was based on the choice of patients with SAH due to a rupture of a cerebral aneurysm that occurred in a period not exceeding 30 days, made by clinical history, brain computed tomography (CT) and cerebral digital angiography. The present study did not include subjects with known endocrine diseases, such as diabetes mellitus.

In all patients, the insulin tolerance test was performed to stimulate GH and cortisol production. The test was protocol with the injection of 0.1 IU/kg insulin (simple), intravenously just after the first blood baseline sample, followed up with a serial collection of samples after 30, 60, 90, and 120 minutes. Before the test, patients remained fasting for 10 hours.

All patients underwent brain CT and cerebral angiography by femoral catheterization.

The values were compared with the reference values and revalidated for conducting the tests on 12 healthy volunteers, 6 men and 6 women, who were known as the control group.

Patients were classified according to the Fisher scale, and after being clinically examined, they were also classified according to the graduation of Hunt & Hess.

In all patients, cerebral tomography was performed to exclude other complications. A digital cerebral angiography confirmed the presence and location of aneurysms.

In five patients, the collection was made pre-and postoperatively, which has given us an opinion on the influence of surgical management in these patients.

For the present work, a design type series of cases was performed. The research was approved by the Ethics Committee of Universidade Federal de Pernambuco (Protocol 227/2002-CEP/CCS) and by the Ethics Committee of the

Hospital da Restauração of Recife. All patients or family are aware of the rules of the research and signed the written informed consent.

The average age of the patients was 48 years old with a median of 50 years old. We used the technique of mathematical logic to extend the model of the network of causes, multivariate analysis, associated with the separation of groups into subgroups or stratum, stratification was observed and the relationship between the dependent variables (hormonal changes) and the independent variables (location of aneurysms, the Hunt & Hess classification, classification of Fisher and the presence of symptomatic cerebral vasospasm).

Statistical Analysis

We applied the statistical test of Kolmogorov-Smirnov to determine the type of distribution of variables to be studied and found that they had non normal distribution. In view of this, we used the nonparametric Mann-Whitney or Kruskal-Wallis tests. In the analysis of categorical variables, we used the Fisher exact test as an alternative to the X2 test (chi-squared), characterizing the level of significance as $< 5\%$ ($p < 0.05$).

Results

The hormone concentrations found in patients with subarachnoid hemorrhage in a period of 30 days after the rupture of aneurysms are shown in ►**Table 1** and ►**Table 2**.

The hormone concentrations found in each of the 21 patients were compared with the normal reference hormonal assay values reported by the laboratory and the values found in the control group (►**Table 3**).

We found abnormalities in most of the hormones studied compared with the reference values of the hormonal assay tests and observed in the control group, with the exception of estradiol, in which no change was observed in any of our patients.

The hormone cortisol is the most changed, and this happened in 52.4% of patients, followed by 42.9% in GH, 28.6% in TSH, 23.8% in T3, 9.5% in prolactin, 9.5% in free T4 and LH, and 4.8% in FSH and T4.

The serum concentration of testosterone was measured in 4 male subjects, and in 3 (75%) it was below normal levels.

It was found that TSH (►**Figure 1**) and GH (►**Figure 2**) showed statistically significant changes ($p < 0.05$). The other hormones, T3, T4, free T4, prolactin, and cortisol, had no statistical differences compared with reference values. The concentration of LH was not significantly affected ($p = 0.114$).

Most of the hormones studied showed changes in deficit, except for patients 5 and 8, in whom the concentrations of basal cortisol and PRL (Prolactin) increased. The importance of ITT (insuline tolarence test) is well-reflected in the changes observed in GH and cortisol, which revealed normal basal concentrations, but inadequate responses to stimulation (patients #3, 4, 5, 6, 11, 12, 13, 14, 15, 16, 18, 19, and 20).

Of the patients studied, the Hunt & Hess classification was 2 (52.4%), 1 (23.8%), 3 (14.3%), and 4 (9.5%). The severity of the subarachnoid hemorrhage was classified in our study according to the scale established by Fisher in 1980 on the CT findings. Three patients were classified with grade 1 (14.3%), 9 patients with grade 2 (42.9%), 6 patients with grade 3 (28.6%), and 3 patients with grade 4 (14.3%).

Aneurysms located in the posterior communicating artery were observed in 8 individuals, equivalent to 42.8% of the sample. The other locations were the middle cerebral artery ($n = 5$; 24.0%), the anterior communicating artery ($n = 5$; 24.0%) and the pericallosal, the basilar, and the posterior inferior cerebellar arteries, with a patient for each of the arteries.

Six out of 21 (28.6%) patients had a history of symptomatic cerebral vasospasm, characterized by somnolence and new motor deficit. Despite the clinical picture of symptomatic vasospasm, all patients progressed to stability and the surgery was uneventful.

Regarding the severity of symptoms of patients with subarachnoid hemorrhage by rupture of cerebral aneurysm, according to the Hunt & Hess scale, hormonal disorder was observed in patients with the more severe clinical picture, Hunt & Hess ≥ 3 with the free T4 ($p = 0.043$). There were also trend changes in T3, TSH, and GH ($p = 0.1$). Sixteen patients presented a Hunt & Hess classification of < 3, and 9 showed hormonal changes corresponding to 56.3% of the sample.

In the Hunt & Hess classification ≥ 3, all 5 patients showed hormonal changes, that is, 100% (patients #5, 6, 8, 13, and 20). According to the Fisher CT classification of subarachnoid hemorrhage used in the present study, we observed significantly higher hormonal disorder in patients with more severe classification in the scale, that is, Fisher 3 and 4, especially for T3 and GH hormones ($p < 0.05$).

Regarding the location of the aneurysm after SAH and the hormonal changes, there was no statistical difference concerning its position, with a slightly greater number of altered hormones in patients with aneurysms located in the anterior communicating artery.

Correlating the hormonal changes due to the subarachnoid hemorrhage of aneurysms located in the polygon of Willis and aneurysms in other locations, the differences were not significant ($p > 0.05$; Fisher exact test). Hormonal changes in the secretion of GH were observed in patients with cerebral vasospasm ($p = 0.041$; Fisher exact test).

From a total of 6 patients with symptomatic vasospasm, 5 (83.3%) showed hormonal changes. The patients with symptomatic vasospasm were numbers 4, 5, 11, 13, 15, and 20. Out of 15 patients who had no vasospasm, 5 showed hormonal changes, representing 33.33% of the cases.

Stratify the patients who presented clinical data compatible with the classification of Hunt & Hess ≥ 3, with patients classified as Fisher ≥ 2, and had cerebral vasospasm; we observed the patient numbers 5, 11, 13, and 20. Of these, three patients (numbers 11, 13 and 20) had an aneurysm of the anterior communicating artery, and there was a higher percentage of hormonal changes in these patients. We

Table 1 Individual data of 21 patients with SAH related to age, genus, and score of the classification of Hunt & Hess, score of the classification of subarachnoid hemorrhage on CT cerebral Fisher and basal concentrations of the following hormones: TSH, T3, T4, FT4, LH, FSH, TESTOSTERONE, ESTRADIOL, PROLACTIN, GH and CORTISOL

Case	Age (years old)/ Sex	Hunt-Hess	Fisher	Angiography	Vasoespasm	TSH (uIU/ml)	T3 (ng/dL)	T4 (ng/dl)	FT4 (ng/dl)	LH (IU/mL)	FSH (IU/mL)	TES (ng/dl)	E2 (pg/mL)	PRL (ng/mL)	GH (ng/ml)	Cortisol (mcg/dL)
1	50/W	II	II	R PComm	No	0.30	80.00	6.40	0.81	24.20	83.10	–	<20.00	6.80	0.12	1.30
2	39/W	II	II	R PICA	No	0.97	86.50	7.10	1.00	6.50	3.60	–	42.30	12.70	0.35	7.70
3	37/M	II	III	ACom	No	0.10	80.80	9.30	1.40	1.50	5.90	53.90	–	3.30	0.16	3.90
4	50/W	II	III	L MCA + L PComm + R PComm	Yes	0.73	46.30	9.70	1.10	15.00	47.80	–	<20.00	15.50	0.31	1.70
5	55/W	IV	III	L MCA	Yes	0.20	48.30	9.80	0.95	21.00	50.60	–	<20.00	51.90	0.91	90.50
6	74/W	III	II	Top of basilar	No	0.63	58.50	6.70	0.68	23.90	65.70	–	31.90	17.00	0.46	25.60
7	58/M	I	II	L Pericalosal	No	0.51	83.50	8.10	1.20	3.10	40.80	–	<20.00	12.70	0.23	11.70
8	40/W	I	III	R MCA	No	0.70	99.60	9.70	1.30	4.20	1.40	113.00	–	78.90	0.41	57.30
9	41/W	I	III	R MCA	No	0.68	77.00	6.10	1.00	1.40	1.20	–	129.00	18.30	0.29	1.70
10	50/M	II	IV	R MCA	No	0.31	84.9	6.90	1.00	3.50	7.20	–	31.90	10.50	0.49	16.50
11	73/M	III	III	ACom	Yes	0.52	100.00	7.40	1.00	3.70	4.40	228.00	–	10.20	1.30	33.90
12	16/M	I	I	R PComm	No	1.27	71.20	6.10	1.10	0.90	1.60	<50.00	–	8.50	1.40	32.50
13	63/W	IV	IV	ACom	Yes	0.21	<40.00	1.20	0.26	0.60	30.90	–	<20.00	9.50	0.54	28.70
14	50/W	II	II	R MCA	No	0.57	92.20	11.00	1.00	7.70	16.90	–	61.60	9.70	1.00	16.10
15	58/W	II	IV	L PComm	Yes	2.45	98.00	7.30	1.30	17.60	65.60	–	<20.00	14.60	0.62	14.60
16	44/W	I	I	R PComm + OA	No	0.47	80.00	4.90	0.93	2.20	2.40	–	45.00	7.00	0.64	1.40
17	46/W	II	II	R PComm	No	0.12	70.00	6.30	0.87	3.90	9.30	–	<20.00	17.80	0.46	5.30
18	30/W	II	II	ACom	No	0.88	76.60	8.20	1.10	0.20	0.20	–	35.10	12.00	1.70	28.70
19	52/W	II	II	R PComm	No	0.82	<40.00	8.60	1.20	47.70	43.90	–	33.70	2.10	0.19	2.00
20	44/W	III	I	ACom	Yes	1.23	97.00	9.50	1.00	2.50	23.80	–	51.30	12.10	0.04	9.80
21	43/W	II	II	L PComm	No	2.20	93.90	6.90	1.20	2.30	9.70	–	88.4	3.10	0.15	16.40

Abbreviations: ACom, anterior communicating artery; CT, computed tomography; E2, estradiol; FSH, follicle-stimulating hormone; FT4, free thyroxine; GH, growth hormone; L, left; LH, luteinizing hormone; M, man; MCA, middle cerebral artery; OA, ophthalmic artery; PComm, posterior communicating artery; PICA, posterior inferior cerebellar artery; PRL, prolactin; R, right; SAH, subarachnoid hemorrhage; T3, triiodothyronine; T4, thyroxine; TES, testosterone; TSH, thyroid stimulating hormone; W, woman.

Table 2 Individual values of hormonal concentrations of prolactin, growth hormone, and cortisol, detected in 21 individuals after the insulin tolerance test, and blood collections were taken at 30, 60, 90, and 120 minutes

	Prolactin (ng/mL)				Growth hormone (ng/ml)				Cortisol (mcg/dL)			
Case	30 minutes	60 minutes	90 minutes	120 minutes	30 minutes	60 minutes	90 minutes	120 minutes	30 minutes	60 minutes	90 minutes	120 minutes
1	9.20	13.20	8.80	8.70	0.16	0.71	3.80	4.10	8.10	4.00	1.40	1.50
2	10.40	9.20	9.80	7.40	3.00	1.70	1.00	1.00	15.90	13.80	13.20	11.00
3	2.60	5.50	6.80	6.80	0.14	0.15	0.30	0.18	3.10	3.20	2.70	2.70
4	13.30	12.90	12.40	14.60	0.30	0.19	0.42	0.45	1.30	1.40	1.50	1.30
5	53.90	53.80	51.80	49.70	0.96	1.00	0.82	0.63	96.40	93.70	89.70	40.80
6	10.00	9.90	6.90	4.30	0.64	0.39	0.47	0.56	26.90	25.90	32.10	34.50
7	11.10	9.10	7.80	12.80	13.10	3.10	0.84	0.45	11.80	17.40	18.70	17.60
8	75.50	74.60	76.70	78.80	6.40	3.64	2.80	1.73	53.40	54.70	60.00	33.70
9	11.10	19.70	18.40	17.50	6.60	3.10	0.42	0.24	2.40	9.70	6.50	1.70
10	10.30	11.90	12.90	12.60	7.15	6.55	4.52	0.42	16.00	19.10	28.90	22.40
11	10.30	20.20	21.40	20.30	9.40	8.50	5.40	3.50	29.50	31.30	35.10	27.30
12	6.90	8.60	10.30	9.60	5.40	2.90	3.90	4.10	16.50	19.40	21.40	12.50
13	5.90	3.30	3.60	3.60	0.72	0.72	0.71	0.62	23.80	25.60	32.90	29.30
14	8.80	16.70	16.80	16.40	3.00	6.70	6.00	6.00	13.00	7.80	8.10	6.30
15	11.20	17.30	38.10	29.10	1.20	1.00	1.80	1.10	16.90	15.40	11.80	15.70
16	9.20	9.40	11.40	10.70	0.53	2.60	5.20	3.60	1.70	1.00	2.20	1.30
17	20.30	17.00	16.00	15.00	5.48	3.90	3.60	3.39	12.10	10.30	9.10	8.70
18	9.00	17.30	5.40	10.30	1.20	1.44	1.60	1.31	33.60	39.70	35.40	33.50
19	5.90	2.10	4.70	4.40	0.23	1.00	0.53	0.50	37.40	34.80	29.30	24.20
20	12.10	13.10	17.40	14.20	0.08	0.80	1.40	0.41	8.10	9.20	8.40	7.60
21	2.20	2.10	1.90	1.50	0.39	10.5	6.50	2.90	10.10	15.00	21.20	17.50

Table 3 Results of tests performed on 12 healthy volunteers

Case	Age (yearsold)/ Sex	T3 (ng/dL)	T4 (ng/dL)	TSH (uIU/ml)	FT4 (ng/dl)	FSH (IU/mL)	LH (IU/mL)	PRL (ng/mL)	E2 (pg/mL)	TES (ng/dl)	GH (ng/ml)	CORTISOL (mcg/dL)
1	53/W	112.00	8.90	2.35	1.00	6.80	2.40	13.00	134.00	–	2.20	17.50
2	55/W	68.90	5.90	1.00	1.10	99.60	23.10	13.30	44.50	–	2.20	9.80
3	51/W	85.80	6.50	1.55	1.20	56.50	24.60	5.40	51.50	–	1.00	5.80
4	45/W	75.40	6.00	0.60	1.00	33.60	13.40	3.60	45.20	–	0.19	11.60
5	50/W	66.30	8.60	0.92	1.00	141.00	55.50	9.70	47.80	–	0.17	2.70
6	36/W	88.10	8.20	01.05	1.20	5.70	8.10	7.70	301	–	0.08	15.90
7	48/M	91.90	4.90	1.16	1.20	2.90	1.10	3.40	–	511.00	0.05	8.10
8	68/M	107.00	9.70	0.64	1.10	7.00	4.70	2.20	–	572.00	0.75	13.00
9	52/M	93.50	6.60	01.09	1.00	1.20	0.50	8.70	–	320.00	0.06	8.80
10	47/M	62.50	8.50	0.90	1.30	1.30	2.10	8.10	–	608.00	0.05	11.60
11	63/M	70.20	7.40	0.82	1.40	8.70	2.00	17.00	–	677.00	0.05	10.50
12	45/M	83.90	5.80	02.05	1.10	5.50	1.90	6.10	–	677.00	0.05	10.50

Abbreviations: E2, estradiol; FSH, follicle-stimulating hormone; FT4, free thyroxine; GH, growth hormone; L, left; LH, luteinizing hormone; M, man; PRL, prolactin; R, right; T3, triiodothyronine; T4, thyroxine; TES, testosterone; TSH, thyroid stimulating hormone; W, woman.

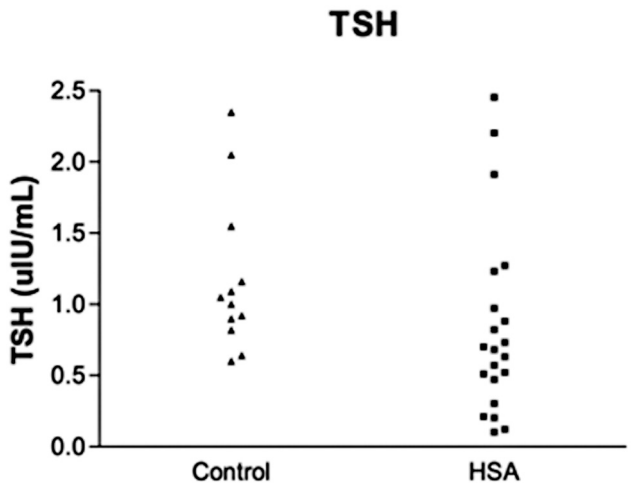

Fig. 1 Comparison between the control group and patients with SAH in the basal dosage of serum TSH ($p = 0.033$).

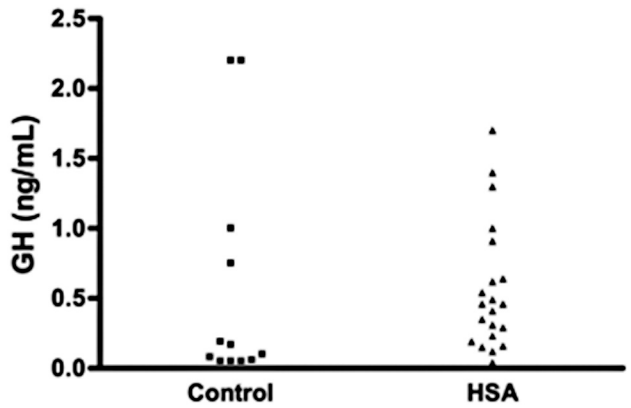

Fig. 2 Comparison between the control group (healthy) and patients with SAH regarding GH ($p = 0.001$).

analyzed the postoperative hormonal dosages in five patients, and normalization occurred in most hormones.

Discussion

Six (29%) of our 21 patients developed cerebral vasospasm with clinical significance of the transient worsening level of consciousness and motor deficit persisting until hospital discharge. These patients had a greater tendency for hormonal changes, and perhaps more significant damage to the hypothalamus-pituitary occurred, consequent to ischemia and increased intracranial pressure.[5]

Our study found 52.4% of patients with changes in cortisol; the majority observed only after the test stimulation of insulin, when there was the expected increase in subsequent doses of 7µg/dl. A subarachnoid hemorrhage by rupture of cerebral aneurysm is the cause of psychological stress, as well as the stress or pain due to increased intracranial pressure.[6] In situations of stress, it is well known that secret the hormone stimulating hypothalamus of corticotropin, which stimulates the pituitary to produce ACTH and the adrenal cortex to stimulate the production of cortisol.[7] With

this condition, it was to be expected that, in this case, find a greater number of patients with increased cortisol. Likely lock in hypothalamus-pituitary axis is involved in our results, as well as specific lesions of the nucleus arched (arcuate) in the tuberal region of the hypothalamus may be involved.[4] Edwards et al.[8] found in their six patients with head trauma, lack of cortisol response to stimulation with the ITT (insuline tolarence test) (0.01 IU / kg), TRH (Thyrotropin-releasing hormone) (200µg) and GnRH (Gonadotropin-releasing hormone) (100µg). Concluded that possible mechanisms are involved, such as direct injury of the hypothalamus by blood in the subarachnoid space, injury to the hypothalamic-pituitary stem the increase in intracranial pressure and decreased cerebral perfusion pressure, or consequent to cerebral vasospasm.[9]

Crompton,[10] in anatomical studies of autopsies of patients with rupture of cerebral aneurysm, observed hypothalamic lesions in 61% of the brains studied. In 2 patients, numbers 5 and 8, we found increased cortisol and prolactin, which is considered a normal response to situations of stress. The prolactin was increased by 9.52% of our patients. It is known that prolactin increases rapidly in situations of stress (2 to 3 times the baseline) and that in 24 hours it returns to normal, as demonstrated in the work of Noel et al.[11] The persistence of hyperprolactinemia may be due to lack of inhibition by damage to the hypothalamus, as demonstrated by Verbalis et al.[12] The other hormonal changes in this study were deficiency in gonadotrophin, thyrotropin, GH and cortisol, data that were also found by other authors.[8,12–15]

The hypothalamic-pituitary-adrenal function, after subarachnoid hemorrhage by rupture of aneurysm, has been evaluated by the diurnal variation of the concentration level of plasma cortisol.[16] The value of plasma cortisol is considered normal when the difference between the highest and lowest dosage from the morning to the afternoon is > 6.4 µg/100ml.[17,18] An abnormal diurnal variation would be a hypothalamic injury, but Jenkins et al.[13] studied 18 patients with SAH by rupture of anterior communicating artery aneurysm with metyrapone test, pyrogen test, and test of suppression with dexamethasone, observing abnormal changes in the diurnal cortisol concentration, control of overhead power and reaction to stress. These authors found normal reaction to stress with the pyrogen test and abnormal response to metyrapone (circadian rhythm). Similar response was found by Krieger[20] using the ITT. They concluded that different sites in the hypothalamus are responsible for the increase in the cortisol response to stress, the circadian rhythm, and the control of feedback. These findings explain the variations in hormonal changes when the subarachnoid hemorrhage affects the hypothalamus. The exact location of these areas has not been determined in humans.[19]

In our study, we found hormonal changes with a predominance of the deficient hormones studied, which is in agreement with other studies.[10,20] Gonadotroph hormones are usually reduced in stressful situations, likely by a hypothalamic effect.[21] Several mechanisms may be involved: the use of illicit drugs, dopamine, glucocorticoids, and opioids may also result in lower levels of gonadotroph hormones (LH, FSH, and thus testosterone, progesterone, and estrogen).[22]

In our study, we found 75% of men with low testosterone. We found no changes in estradiol. A decrease of LH was found in 9.5% of patients and a decrease of 4.6% of FSH were observed in this series. These findings disagree with the literature that indicates a percentage of 67.5% of changes.[15] Despite these studies having emphasized the hormonal changes found in patients with rupture of cerebral aneurysm caused by subarachnoid hemorrhage, Osterman[23] evaluated the hormonal function of 50 patients with SAH and cerebral aneurysm in one, due to arteriovenous malformation and occipital pattern found normal circadian cortisol in 47 patients. The function and levels of gonadotropin were normal in all patients. These patients were examined 105 days after subarachnoid hemorrhage.

The findings of Osterman[23] disagree with the literature review by Fernández-Real et al.[15] These authors investigated the pituitary dysfunction caused by aneurysm of the carotid artery, as follows: pituitary gonadal dysfunction in 67.5% of cases, pituitary-adrenal in 48.6%, and pituitary-thyroid in 40.5% of cases.

Analyzing the results of our study, patients who presented with greater clinical severity (Hunt & Hess ≥ 3) showed a greater number of hormonal changes; however, statistically, only free T4 was significantly different ($p = 0.0476$) when compared with the group of Hunt & Hess 1 and 2. As for CT findings, according to Fisher's classification, major hormonal changes were observed in patients with Fisher CT classified as 3 and 4, and the hormone GH was statistically significant ($p = 0.0004$), as well as T3 ($p = 0.0062$). We also observed a greater tendency for hormonal changes in patients with aneurysms located in the anterior communicating artery, and those who had cerebral vasospasm, and in the latter, GH was statistically significant ($p = 0.0464$).

After stress, the GH tends to increase the metabolism by releasing of peptides (somatomedina)[24] In our study, we found 42.8% of patients with decreased GH response to stimulation with insulin. Some authors suggest that the decrease in the production of GH, which also occurs in severe head injuries, is caused by direct damage to the hypothalamus or by vascular spasms.[11,18,25] Colon et al.[25] showed the importance of GH on cognitive function in adults, showing the great importance of the preservation of these hormones at all ages.

Stress reduces the level of TSH and increases the level of cortisol.[26] Mangieri et al.[27] examined the hormonal changes of 38 patients with SAH caused by rupture of cerebral aneurysms within the first 24 hours after SAH, and observed an increase in cortisol in all patients, increased prolactin in 14.2% of patients, normal levels of FSH and LH and increased levels of TSH in 14.2% of patients, concluding that the hormonal abnormalities observed in measurements may be due to the stress caused by intracranial bleeding.

The decrease in the level of TSH in a patient under stress is due to the production of interleukin I and somatostatin,

as well as the result of increased cortisol.[28] Peters et al.[29] demonstrated that in peripheral tissues, there is metabolism of T4 to T3 by the type 1 deiodinase enzyme, which is blocked by cortisol under stress. Gupta et al.[30] reported that central hypothyroidism is characterized by low thyroid hormone with good response to stimulation of TSH to TRH, which reflects lack of stimulation of the hypothalamus.

We found in our study a decrease of 28.57% of patients for TSH, 23.80% for T3, T4 to 9.52% and 4.76% for free T4. Patients number 1, 10, and 17 showed decreased TSH and normal levels of T3, T4 and free T4, which is consistent with reaction to stress. Patients number 5 and 13 showed low levels of TSH, T3, T4 and free T4. We don't found justification for such an occurrence. Although these findings are true from the perspective of percentage, one should be careful with their interpretation, since hormonal changes are not statistically significant, with a confidence interval (CI) of 95% ($p < 0.05$) in TSH hormones, testosterone, and GH.

Other factors of importance related to our research are the recent published work showing the great relationship between quality of life, with improvement of cognitive functions (affection, mood, memory, etc.) and treatment of specific hormonal deficiency, avoiding in some cases, the frequent downtime and dementia in patients with deficiency of this hormone.[31,32]

Disorders of sodium balance after SAH are common electrolyte disturbances. Hyponatremia can affect up to 55% of patients with SAH and tends to be more frequent than hypernatremia.[33,34] Hypernatremia occurs in 20% of patients with SAH.[33] Both sodium disorders are associated with worse neurological outcomes, especially hypernatremia.[35–39] Furthermore, a recent cohort study showed that greater variability of sodium concentration is also associated with poor neurological outcome.[40] However, sodium disorders are apparently not associated with an increased risk of vasospasm after SAH.[39]

The present research report provides the risk factors for the development of hormonal changes in patients with SAH due to rupture of a cerebral aneurysm;

a) The higher the ranking by the clinical scale of Hunt & Hess ($\geq$ 3), the greater the possibility of hormonal changes.
b) The larger the changes in tomographic studies of Fisher ($\geq$ 2), the greater the possibility of hormonal changes.
c) The location of the aneurysm in the anterior communicating artery increases the possibility of hormonal changes.
d) The presence of cerebral vasospasm is the factor most likely to cause hormonal changes.

Conclusion

The present research reveals the existence of hormonal changes of the hypothalamic-pituitary axis in SAHs by rupture of intracranial aneurysm, statistically significant for the hormones GH, TSH, free T4 and testosterone.

Conflict of Interests
The authors have no conflict of interests to declare.

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