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EVALUATION OF PITUITARY AND THYROID HORMONES IN PATIENTS WITH SUBARACHNOID HEMORRHAGE DUE TO RUPTURED INTRACRANIAL ANEURYSM

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ABSTRACT - It is well known that the central nervous system (CNS) influences the pituitary hormone secretions and that diseases of CNS are frequently associated with an altered endocrine function. The aim of this study has been the evaluation of the serum concentrations of the pituitary and thyroid hormones in a series of patients with subarachnoid hemorrhage due to a ruptured cerebral aneurysm. Thirty-five patients (23 females and 12 males), aged 51.9±13.3 years on the mean were admitted. They were evaluated to assess the clinical severity of the subarachnoid hemorrhage by Hunt & Hess scale: nine patients were in the grade I, 14 in the grade II, and 12 in the grade III. Blood samples were obtained between 8:00 and 9:00 a.m. and serum hormones were measured by commercial kits (IRMA or MEIA methods). Cortisol serum levels (normal range (NR) = 5 to 18 μg/dL) were increased in all the patients (mean ± standard deviation = 31.4±12.4 μg/dL). Mean prolactin levels (NR < 20 ng/mL) were 18.6±17.1 ng/mL and five patients (14.2%) had levels higher than normal. FSH and LH levels were normal according to age and sex: men: FSH = 4±2.9 mUI/mL (NR = 1 to 10.5 mUI/mL); LH = 6.1±6.3 mUI/mL (NR = 2 to 12 mUI/mL); premenopausa women: FSH = 2.5±1.5 mUI/mL (NR = 2.4 to 9.3 mUI/mL); LH 3.9±5.1 mUI/mL (NR =2 to 15 mUI/mL); post- menopausal women: FSH = 48.3±18.5 mUI/mL (NR =31 to 134 mUI/mL); LH = 29±13.8 mUI/mL (NR =16 to 64 mUI/mL). Mean TSH levels were 3.9±5.2 μUI/mL (NR =0.5 to 4.7 μUI/mL) and five patients (14.2%) had levels higher than normal. Mean triiodothyronine levels (T3) were 66.4±18.7 ng/dL (NR = 45 to 137 ng/dL) and five patients (14.2%) had levels lower than normal (33.8±9 ng/dL). Mean thyroxine levels (T4) (NR= 4.5 to 12.5 μg/dL) were 7.4±1.7 μg/dL and two patients (5.6%) had levels lower than normal. Thyroglobulin and microsomal antibodies were not detectable. Conclusions: In the first 24 hours following ictus, the hormonal changes may be due to the stress produced by the intracranial bleeding; thyroid hormone alterations suggest that patients with subarachnoid hemorrhage might have an euthyroid sick syndrome.

KEY WORDS: cerebral aneurysm, subarachnoid hemorrhage, pituitary, thyroid hormones, euthyroid sick syndrome.

Avaliação dos hormônios hipofisários e tireoidianos em pacientes com hemorragia subaracnoidea devido a ruptura de aneurisma intracraniano

RESUMO - É bem conhecido que o sistema nervoso central (SNC) influencia as secreções dos hormônios hipofisários e que doenças do SNC são frequentemene associadas com função endócrina alterada. O objetivo deste estudo foi avaliar as concentrações séricas dos hormônios hipofisários e tireoidianos em uma série de pacientes acometidos de hemorragia subaracnóidea devida a ruptura de aneurisma cerebral. Foram avaliados 35 pacientes (23 mulheres e 12 homens), com média de idade de 51,9±13,3 anos. Foram avaliados para a severidade da doença pela escala de Hunt & Hess: nove deles estavam no grau I, 14 no grau II e 12 no grau III. As amostras de sangue foram obtidas entre 8:00 e 9:00 horas e os hormônios foram medidos pelos métodos de IRMA ou de MEIA. Os níveis séricos de cortisol (valor normal (VN) 5 a 18 μg/dl) estavam aumentados em todos os pacientes (média±desvio padrão = 31,4±12,4 μg/dl). Os níveis de prolactina (VN <20 ng/ml) foram de 18,6±17,1 ng/ml e cinco (14,2%) tiveram níveis maiores do que o normal. Os níveis de FSH e LH foram normais de acordo com a idade e sexo: homens – FSH = 4,0±2,9 mUI/ml (VN =1 a 10,5 mUI/ml); LH = 6,1±6,3 mUI/ml (VN =2 a 12 mUI/ml); mulheres – pré-menopausa: FSH = 2,5±1,5 mUI/ml (VN =2,4 a 9,3 mUI/ml); LH 3,9±5,1 mUI/ml (VN =2 a 15 μUI/ml); pós-menopausa: FSH = 48,3±18,5 mUI/ml (valor normal =31 a 134 mUI/ml); LH = 29±13,8 mUI/ml (VN =16 a 64 mUI/ml). Os níveis de TSH foram 3,9±5,2 μUI/ml (VN =0,5 a 4,7 μUI/ml) e cinco pacientes (14,2 %) tiveram níveis maiores do que o normal. Os níveis de triiodotironina

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(T3) foram de 66,4±18,7 ng/dl (VN = 45 a 137 ng/dl) e cinco pacientes (14,2%) tiveram níveis menores do que o normal (33,8±9 ng/dl). Os níveis de tiroxina (T4) (VN= 4,5 a 12,5 μg/dl) foram de 7,4±1,7 μg/dl e dois pacientes (5,6 %) tiveram níveis menores do que o normal. Anticorpos antitireoglobulina e antimicrossomal não foram detectados. Conclusões: nas primeiras 24 horas seguindo o quadro ictal, as anormalidades observadas nas dosagens hormonais podem ser devidas ao estresse provocado pelo sangramento intracraniano; as alterações observadas nos hormônios tireoidianos sugerem que os pacientes com hemorragia subaracnoidea podem desenvolver a síndrome do doente eutireoideo.

PALAVRAS-CHAVE: aneurisma cerebral, hemorragia subaracnóidea, hipófise, hormônios tireóideos, síndrome do doente eutiróideo.

Spontaneous subarachnoid hemorrhage is a sudden blood extravasation in the subarachnoid space due to a blood vessel rupture, occurring more frequently at the level of a cerebral aneurysm[1,2]. The incidence of the disease is 10 cases for 100 000 inhabitants, 56% in women, most frequently between the fifth and sixth decades[1,2]. Mortality before arriving at the hospital can reach 50% and is about 20% in the hospitalized patients[2]. Subarachnoid hemorrhage due to a ruptured intracranial aneurysm is associated with sudden headache, vomiting, loss of consciousness, stiff neck and paralysis of cranial nerves[1,2]. The initial sudden headache is present in 91.3% of the patients and it is defined as unbearable and anguish, caused by alterations in the intracranial pressure. These signs and symptoms produce a distressing sensation of sudden death in the patient[2].

It has been shown that acute and chronic stress situations produce alterations in the hormonal secretion. Stress produces its effects on the endocrine system by still poorly defined central pathways that stimulate the hypothalamus to release its secretagogues hormones at the level of the median eminence[3,4]. Major stresses, as important surgeries, traumas, hypovolemia, infections and intense pain increase hypothalamus-pituitary-adrenal axis activity producing corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol hypersecretion. Morever, in these situations the day/night pattern of the ACTH - cortisol secretion and the negative feedback of the glucocorticoids appear to be disrupted[5,6]. The increased CRH and antidiuretic hormone (ADH) secretion during stress can also be responsible of the decreased gonadotrophin releasing hormone (GnRH) release and, consequently, of the pituitary gonadotrophin - FSH and LH- secretion. This effect can be mediated by opioid endogenous peptides that are also increased during stress[7]. Acute stress might also induce hyperprolactinemia and this can have some effect on the immune system and on the maintenance of the glycemic levels[3]. On the other hand, decreased TSH levels have been described during stress possibly due to increased somatostatin and interleukin 1 production[4].

Neoplasic, inflammatory or vascular diseases involving the hypothalamus and/or the pituitary gland, as well as surgical and radiotherapic treatments of these structures have been reported to increase TSH serum levels[8] and to produce a plurihormonal deficit of the pituitary hormones[9].

Due to the important interactions between the central nervous system (CNS) and the endocrine system, particularly in stressfull situations as a spontaneous subarachnoid hemorrhage by ruptured cerebral aneurysm, we have analyzed the hormonal secretion profile of the major endocrine axes in the first 24 hours following an acute subarachnoid hemorrhage.

METHOD

Patients - Thirty-five subjects of both sexes were recruited from January of 1998 to July 1999 from patients hospitalized for spontaneous subarachnoid hemorrhage due to ruptured cerebral aneurysm in the Neurosurgery Unit of the "Hospital de Base do Distrito Federal". This is the principal public hospital with a neurosurgery unit of area of Brasília covering a user population of two millions of people.

The diagnosis of spontaneous subarachnoid hemorrhage was accomplished by anamnestic and physical findings and by brain computerized tomography. The presence of the aneurysm was determined by four-vessel conventional x-ray angiography (both carotids and both vertebrals), through femoral artery catheterism.

At admission to the hospital the patients were evaluated clinically and classified according to the Hunt & Hess scale which is used exclusively in patients with spontaneous subarachnoid hemorrhage for clinical and prognostic assessement[10]. All the patients were followed until discharged from hospital. Before discharge they were also evaluated by the prognostic Glasgow scale[11].

The inclusion criteria utilized were: spontaneous hemorrhage subarachnoid due to ruptured cerebral aneurysm (grade I to III in the Hunt & Hess scale); absence of associated sistemic diseases, such as renal, heart, respiratory failure and diabetes mellitus. The exclusion criteria were: non aneurysmatic spontaneous subarachnoid hemorrhage; patients classified in grade IV and V of the Hunt & Hess scale; patients previously using confounding drugs, as the replacement hormonal therapy of any type.

Hormonal assays - Blood samples were collected between 8 and 9 AM, within 24 hours from ictus, centrifuged at 3000 rpm, for 10 minutes, and the serum stored at –20 C until assayed. Commercial "kits" were used: T3, T4, TSH and cortisol were assayed by immunofluorimetry (Autodelphia - São Paulo); FSH by microparticles enzymatic immunoassay (MEIA) (Abbott–São Paulo); LH and prolactin by an immunoluminescence assay (Elecys–São Paulo); antithyreoglobulin and antimicrossomal antibodies by indirect hemoagglutination (Bayer - São Paulo).

Statistical analysis - Data were analyzed by the analysis of the variance (ANOVA) utilizing the Dunnett test for comparisons; the level of significance was fixed at $p < 0.05$. The results are presented as mean ± standard deviation (M±SD).

This study was approved by the Committee of Ethics in Research of the "Secretaria de Saude do Distrito Federal". Patients or their legal representatives signed the informed consent for participation in the study.

RESULTS

Thirty-five patients entered the study: 23 females and 12 males, aged 51.9±13.3 years on average. The difference between the age of females (52.5 ±14.8 years) and of males (51± 3.3 years) was not statistically significant. The location of the aneurysms is shown in Table 1. Nine patients were classified in grade I of the Hunt & Hess scale (asymptomatic or with minimal to discrete headache), fourteen in grade II (moderate to severe headache, stiff neck and absence of focal neurological signs, except cranial nerves paralysis) and twelve in grade III (sleepiness, mental confusion and discreet focal neurological deficits).

As shown in Table 2, cortisol levels were increased in all the patients and no difference was observed between the mean values present in the different sexes. Prolactin levels were significantly lower in men than in women ($p < 0.05$) (Table 2). Five patients (14.2%) had prolactin levels above the normal range. FSH and LH levels were normal for age and sex. As expected, the post-menopausal women showed significantly higher FSH and LH levels than the pre-menopausal ones (Table 2).

TSH, T3, and T4 levels were similar in men and in women (Table 2). Five patients (14.2%) had TSH levels higher than normal. T3 levels were lower than normal in five patients (14.2%), with a mean value of 33.8±9 ng/dL. The levels of T4 were low in two patients (5.6%). Antithyreoglobulin and antimicrosomal antibodies were not detected in any patient.

Table 1. Distribution of the cerebral aneurysms in 35 patients with subarachnoid hemorrhage due to spontaneous rupture of a cerebral aneurysm.

Artery	cases (n)	%
Anterior communicans	12	34.2
Posterior communicans	6	17.1
Media cerebri	5	14.2
Multiple aneurysms	5	14.2
Other locations	7	20

Table 2. Hormone levels in 35 patients with subarachnoid hemorrhage due to ruptured cerebral aneurysm (M ± SD).

Hormones (normal range)	Female (n = 23)	Male (n = 12)	Total (n = 35)
Cortisol (5 to 18 μg/dL)	25.5±14	28.8±11.4	31.4±12.4
Prolactin (< 20 ng/mL)	19.3±17.9 *	11.9±0.2	18.6±17.1
FSH (1 to 10.5 mUI/mL)	-	4±2.9	-
Pre-menopause (2.4 to 9.3)	2.5±1.5	-	-
Post-menopause (31 to 134)	48±18.5 * *	-	-
LH (2 to 12 mUI/mL)	-	6.1±6.3	-
Pre-menopause (2 at 15)	3.9±5.1	-	-
Post-menopause (16 to 64)	29(13,8 * *	-	-
TSH (0.5 to 4.7 μU/mL)	3.7±4.8	2.6±1.7	3.9±5.2
T3 (45 to 137 ng/dL)	66.9±19.2	66.6±18.7	66.4±18.7
T4 (4.5 to 12 μg/dL)	7.1±1.8	7.8±1.6	7.4±1.7

* $p < 0.05$ Vs male; * * $p < 0.05$ Vs pre - menopause

Evolution: All the patients were submitted to surgical treatment. Most (70%) of the patients were finally classified in grade 4 and 5 of the prognostic Glasgow scale. Two deaths occurred: one for rupture of the aneurysm during surgery and the other for lung infection.

DISCUSSION

The increase of the cortisol in all our patients probably reflects the high level of stress produced by the subarachnoid hemorrhage due to the ruptured aneurysm; it is probably produced by a combination of psychological stress and pain, with the possibile involvement of the hypotension and hypovolemia. Increased levels of cortisol has been described in other types of intense stress, such as severe trauma, burns, important surgery, hypotension and serious systemic diseases[12,13]. The intense stress exerts its effects by not well defined central pathways which stimule the CRH neurons located in the hypothalamus to secrete CRH in the pituitary portal system. ACTH is then hypersecreted by the pituitary gland, stimulating in its turn cortisol liberation by the adrenal glands[14]. The intense stress disrupts the day/night pattern of the ACTH and cortisol secretions, and abolishes the negative feedback of cortisol at the hypothalamic-pituitary level[5,6,15].

Antidiuretic hormone (ADH) and norepinephrine are other ACTH secretagogues that acts sinergistically with CRH in the regulation of the response to stress[14]. On the other hand, endorphinergic fibers are part of the stress pathways involved in the cortisol and ACTH responses, as it has been shown to occur in major surgeries[16].

The increase of the cortisol during the stress certainly represent a vital mechanism of defense of the organism in the maintenance of the homeostasis in these situations. The glucocorticoids can rapidly induce alterations of the excitability of the neuronal membranes[17]. They may also affect the cerebrovascular permeability and the choroidal transport of water and electrolytes, being important in the regulation of the synthesis of liquor and in the brain volume homeostasis[4]. Complex interactions between the hypothalamus-pituitary-adrenal axis and the immune system can also have a fundamental physiological importance in the stress reponse[18]. Glucocorticoids produce a multistep inhibition of the immune system protecting the organism from the consequences of excessive inflammatory reactions[15,18,19].

Prolactin levels were significantly higher in the women than in the men. This fact is not surprising since estrogen levels are higher in women and represent a strong stimulus for prolactin secretion[20]. Estrogens stimulate mRNA production and the prolactin synthesis in the pituitary gland and also promote the mitotic activity of lactotrophs. It has been reported that acute stress increases prolactin levels[21]. However, we observed that only a minority of our patients had high prolactin levels, but this can be due to a too late withdrawal of the blood sample after the acute ictal episode (within 24 hours). As a matter of fact it is known that prolactin, after an acute stress, reaches a peak which exceedes two to three times its basal levels, but it rapidly goes back to the normal level within one hour[21]. Moreover, the prolactin increase might have been limited by the concomitant increase of the cortisol observed in all our patients. It has been described that the prolactin secretion provoked by stress in adrenalectomized mice results in a longer lasting increase in prolactin[22,23].

Endogenous opioid peptides are probabily involved in the mechanism of stress induced hyperprolactinemia, since it has been shown that the naloxone, an opioid antagonist, blocks to a large extent prolactin levels following surgical stress [24]. The physiological role of prolactin hypersecretion during the acute stress is not clear; some beneficial effects on the immune system[3,25] and on the maintenance of the glycemic levels[3] have been proposed.

We did not record in our patients alterations of FSH and LH levels, both in men and in women. This observation is to a certain extent in disagreement with the data of the literature. It has been reported that stress frequently causes menstrual alterations, mainly amenorrhoea, with low or normal FSH and LH levels, associated with low or normal estrogen secretion suggesting a possible effect at the hypothalamic level[26]. Moreover, the development of hypogonadotrophic hypogonadism is common during acute diseases[27]. However studies in subjects hospitalized for cranial traumatisms, acute myocardium infarction and surgery have shown that the most significant decrease of FSH occurs two days after the beginning of the stress and that the reduced LH secretion only after four days[28]. Since the blood samples of in our study were never obtained later than 24 hours after ictus it is possible that is this short time interval explains the apparent discrepancy. Moreover, the use of drugs, such as dopamine, glucocorticoids and opioids, in acutely sick patients, can also contribute to the decrease of LH and testosterone[29] secretion, and these drugs were not used in our patients. Finally it has been shown that the

alterations in FSH and testosterone levels, but not of LH, are correlated with the severity of the disease measured by the APACHE score (Acute Physiology and Chronic Health Evaluation)[29] and our patients, being all included in grade I to III of the Hunt & Hess classification, were not so seriously health compromised.

The great majority of our patients did not presented alterations in TSH, T4, and T3 secretions; only five patients showed high TSH levels, other five decrease T3 and two low T4. Antithyrod antibodies were never present. Even if it is not possible to completely exclude the possibility of an associated thyroid disease in our patients, the absence of antibodies against thyroid might be considered as indicative of the absence of primary hypothyroidism[30]. Increased levels of TSH have been described in patients with serious sistemic diseases[31,32], with hypothalamic and pituitary tumors[8,9,30,33], following surgery or cerebral radiotherapy[8] often producing diagnostic confusion with primary hypothyroidism[8].

The observation that the great majority of our patients have normal TSH levels and none shows suppressed levels of the hormone is somehow surprising, since it has been reported that the stress produces a decreased TSH secretion, effect mediated by the somatostatin and interleukin 1[4,34]. Morever, cortisol levels were increased in all the patients and this hormone has a known inhibitory effect on TSH secretion. Pharmacological doses of glucocorticoid reduce TSH secretion in normal and hypothyroid patients, blunt the TSH response to TRH and abolish the night increase of TSH[34-36]. Hydrocortisone infusions, simulating the levels of cortisol present during moderate stress, suppress TSH secretion[35]. Finally, the levels of TSH are more elevated in patients with adrenal insufficiency and they decrease during the physiologic replacement therapy with glucocorticoids[36]. Even if we have not observed a decreased TSH secretion, this does not exclude the possibility that the high cortisol levels have affected TSH secretion in our patient with subarachnoid hemorrhage. This because the low T3 and T4 levels observed in some patient was not accompanied by the normal compensatory increase of the TSH levels. This observation suggests that some degree of inhibition of the TSH secretion could have been exerted by the high cortisol levels in these patients.

The presence of low T3 or low T4 levels, with a normal TSH concentration (and absence of antithyroid antibodies) in the first hours following ictus, suggests that a small group of patients with subarachnoid hemorrhage might have an euthyroid sick syndrome[37,38]. This syndrome is characterized by a decreased serum T3, increased reverse T3 levels, associated or not to normal TSH and T4 levels[37,38]. The low T3 serum concentrations are due to a decreased conversion of T4 to T3 in the peripheral tissues, including liver and kidneys, that are the major responsibles of circulating T3[37,38]. The inhibition of the iodotironinedeiodinase type I, that metabolizes T4 to T3, can be due to the high cortisol levels found in our patients with subarachnoid hemorrhage, since pharmacological doses glucocorticoid block the conversion of T4 to T3, increasing the conversion of T4 to reverse T3[34,39]. It is therefore possible that the alterations observed in our patients and that is characteristic of euthyroid sick syndrome may be due to the high cortisol levels.

In conclusion, the hormonal abnormalities observed in the first 24 hours following ictus in patients with subarachnoid hemorrhage can be produced by the stressful stimulus provoked by the intracranianial bleeding. The high cortisol levels observed in all the patients can have an important role in producing these hormonal alterations. It is possible that some patient develops an euthyroid sick syndrome.

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