Anterior Pituitary Hormones Changes After Spontaneous Subarachnoid Hemorrhage

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Citation

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Abstract
BACKGROUND & OBJECTIVES:
Due to the important interactions between the central nervous system and the endocrine system, particularly in stressful situations as spontaneous subarachnoid hemorrhage (SAH), several changes have been described regarding anterior pituitary dysfunction during the course SAH.

PATIENTS & METHODS:
The anterior pituitary functions of 30 consecutive patients (11 males and 19 females) were tested both in the first week and after 3 months following SAH. The following hormones were measured in all patients: thyroid-stimulating hormone (TSH), free thyroxine (free T4), Triiodothyronine (free T3), luteinizing hormone (LH), follicle-stimulating hormone (FSH), Prolactin (PRL), serum cortisol, plasma adrenocorticotropic hormone (ACTH) and growth hormone (GH).

RESULTS:
30 patients with a mean age (53.93 ±6.36 SD), 36.7% males, 63.3% females. 28 (93.3%) had aneurysmal SAH and 2 (6.7%) patients caused by AVM. 60% managed surgically by clipping, 23.3% by coiling and 6.7% by embolization of AVM. Within the 1st week, 16 (53.3%) patients showed pituitary deficiency (PD),8 (26.7%) had single hormone deficiency, 6 (20%) 2 hormones deficiency, 1 (3.3%) 3 hormones and 1 (3.3%) 4 hormones deficiencies. FSH and LH deficiency was the most frequent (33.3%). 8 (26.7%) patients had hydrocephalus and 7 of them (87.5%) had PD. All patients experienced vasospasm had PD. Follow up was conducted on 27 patients, 10 (37%) had PD, 7 (25.9%) single axis deficiency and 3 (11.1%) double axis deficiencies. FSH and LH deficiency = 25.9%, GHD = 14.8%, both cortisol and TSH deficiency = 3.7%. Neither ACTH nor prolactin deficiency was identified on follow up.

Conclusions:
Pituitary dysfunction was identified in a substantial portion of patients with SAH, gonadotropins and GH deficiencies persisted over time but no association was found between this dysfunction and poor clinical outcome. Patients with hydrocephalus / vasospasm are at high risk of subsequent hypopituitarism.

INTRODUCTION:
Spontaneous subarachnoid hemorrhage (SAH) is a common and devastating neurological condition. Its incidence varies from region to region; the aggregate worldwide incidence is about 10.5 cases per 100,000 people per years1. Its incidence increases with age, occurring most commonly between the 4th and 6th decade. It is 1.6 times more frequent in women than men. The most common cause of SAH is a ruptured aneurysm. Hypertension, smoking, female gender, and heavy alcohol use have been implicated as the strongest risk factors associated with this condition 2.

The mortality associated with SAH ranges from 40 to 50% and many survivors report problems with memory, mood, fatigue, headaches, and cognitive impairment1. These patients suffer from chronically disabling symptoms impairing their quality of life 3. Several clinical studies have provided evidence that hypopituitarism is a common
complication of aneurysmal subarachnoid haemorrhage 4. SAH poses serious risk for pituitary dysfunctions due to proximity of hypothalamo-pituitary complex to the circle of Willis. Direct compression by the aneurysm, vasospasm, high intracranial pressure, or surgical manipulation may lead to subsequent hypopituitarism 5.

With this background, we conducted a study to know the real incidence of endocrine abnormalities in our population related to the anterior pituitary gland in patients presenting with spontaneous SAH both in acute stage and after three months post-SAH.

**MATERIAL AND METHODS:**

This is a prospective cohort study of thirty patients of spontaneous subarachnoid hemorrhage who presented at the Mansoura University Hospitals between September 2014 and December 2015. This study was approved by the ethical and research committee of the Mansoura University. All patients have given written informed consent for procedures and publication.

Patients with known endocrine abnormalities, liver or kidney diseases and patients aged less than eighteen years, and cases of traumatic subarachnoid hemorrhage were not included in this study.

All patients were admitted to the ICU for close observation. CT angiography and CT brain were done to discover the cause of SAH. Severity of SAH was graded clinically by the Hunt & Hess scale and radiologically by the Fisher classification. Every possible effort was made to keep the patients in normothermic, normoglycemic state and in electrolytes balance. The mean arterial pressure was kept between 90–140 mm Hg before and <200 mm Hg after aneurysmal treatment. All patients received Nimodipine 60 mg every 4 hourly for 21 days.

As per protocol, a panel of anterior pituitary hormones was obtained soon after admission. Posterior pituitary hormones were not tested. Commercially available kits were used to determine hormone levels like adrenocorticotropic hormone, growth hormone, thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, prolactin, insulin growth factor, thyroxine, triiodothyronine, cortisol and testosterone.

Four vessels cerebral angiography was done in selected cases of cerebral aneurysms and in all patients with AVM to know the anatomy, location and feeders of aneurysms and AVM. Clipping of aneurysms/excision of AVM by open surgery or coiling and embolization, both options were given to all patients and their families. Postoperative CT and CTA brain were also done in all patients to check the status of clips.

Three patients died pre-operatively due to their high clinical Hunt and Hess grade and low GCS. The remaining patients were discharged in satisfactory condition and were advised to do follow up on monthly basis up to three months. During their last visit, another panel of hormonal profile of the anterior pituitary gland was taken to compare with the samples taken at the time of admission, and to see any relationship with any complications of SAH.

SPSS software (serious 10, 2002) was used to analyze the data. Data changes will be compared with the basic reading of the studied patients using paired T-Test for numerical results and Chi-square test for non-numerical data value.

**RESULTS:**

Among 30 patients, 11 were males (36.7%) and 19 were females (63.3%). The mean age was 53.9. Hypertension was recorded in 20 patients (66.7%), diabetes mellitus in 7 patients (23.3%) and only 3 patients (10%) were found to be smokers.

Aneurysms were responsible for SAH in 28 cases and AVM only in two cases. In the aneurysmal subgroup, 12 cases (40%) had an aneurysm of the anterior communicating artery, 7 cases (23.3%) of the internal carotid artery and 9 cases (30%) of the middle cerebral artery.

Microsurgical clipping was done in 18 cases and endovascular coiling in 7 cases. Both cases of AVM underwent endovascular embolization. Three cases (10%) developed vasospasm and eight patients (26.7%) developed a hydrocephalus which was managed by either external ventricular drain or ventriculo-peritoneal shunt.

Hormonal profiles showed hypopituitarism in 16 patients (53.3%). FSH/LH deficiency was the most frequent disorder (33.3%), followed by GH (26.7%), TSH (6.7%), ACTH (6.7%) and prolactin (6.7%). Eight (26.6%) patients showed disturbances in more than one axis. Two hormonal deficiencies were seen in six patients and one showed 3 hormonal deficiencies and another one with 4 hormones deficiencies. After three months, 10 patients showed persistent endocrine abnormalities, seven had single hormonal axis deficiency and 3 had double axis deficiency.
Patients with high cortisol level during acute phase (20%) showed normalization of their cortisol level after 3 months. TSH deficiency was noted in 2 patients (6.7%) in the acute stage and in 1 patient (3.3%) during follow up. No association was found between TSH deficiency and hydrocephalus or vasospasm in the acute stage or in the follow up. Hyperprolactinemia was noted in one male patient (3.3%) and deficiency was detected in 2 female patients (6.7%) in the acute stage. During follow up all patients had normal prolactin levels. No association was found between prolactin disturbances and presence of hydrocephalus or vasospasm. Low IGF1 was detected in 8 patients (26.7%) in the acute stage and in 4 patients (13.3%) during follow up. Five out of eight patients had low IGF1 in the acute stage presented also with hydrocephalus which results in a significant relationship between presence of hydrocephalus and low IGF1 levels in the acute stage (p=0.007).

### Table 1

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<th>Hormonal abnormalities in the acute stage</th>
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<td>One Axis Deficiency</td>
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<td>Four Axes Deficiency</td>
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<td><strong>Total</strong></td>
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### Figure 1

Pituitary axes changes in the acute and follow-up periods

### Table 2

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<th>Hormonal abnormalities at 3 months follow-up</th>
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A 44 year old morbidly obese female with known hypertension presented with acute severe headache; A: Non contrast CT brain axial cut showed diffuse SAH with intraventricular extension into the third ventricle, B: CT angio brain volume rendering transparent formats processed image showed wide neck AcomA aneurysm with dominant left A1, C, D, E, F: Intraoperative photos showing the AcomA aneurysm before and after successful clip application, G: Postoperative non contrast CT brain axial cut showed the surgical corridor from right pterional approach and aneurysm clip in position, H, I, J: Postoperative CT angio brain showing successful exclusion of the AcomA aneurysm and clearly reconstructed bifurcation; H: Sagittal reformat, I: 3D volume rendering processed image with titanium aneurysm clip in place, J: volume rendering processed image without clip, K, L: Postoperative Angiogram, 3D and 2D images confirming stable occlusion of the AcomA aneurysm one year after the surgery.
Anterior Pituitary Hormones Changes After Spontaneous Subarachnoid Hemorrhage

Figure 3
A 28 year old male presented with acute severe headache; A: Non contrast CT brain axial cut showed diffuse SAH, B, C, D: CT angio brain axial, sagittal and volume rendering format processed images showed wide neck small pyramidal AcomA aneurysm with dominant left A1, E, F: Intraoperative photos showing the AcomA aneurysm before and after successful clip application at the aneurysm neck, G, H: postoperative CT angio brain showing successful exclusion of the AcomA aneurysm and clearly reconstructed bifurcation; G: Axial, H: coronal reformat processed image with Codman aneurysm clip in place, J, K, L: postoperative Angiogram, 2D left ICA Lat & A-P and 3D right ICA angiogram images confirming stable occlusion of the AcomA aneurysm six months after the surgery.

Figure 4
A 53 year old female presented by acute severe headache followed by acute confusional state; A&B: Non contrast CT brain axial cut showed diffuse SAH with intra-ventricular extension into the septum pellucidum, C&D: CT angio brain volume rendering& transparent formats processed image showed narrow neck, small AcomA aneurysm with dominant left A1, E&F: Digital subtraction angiography working view pre-coiling and post-coiling with complete obliteration (CO), G: Digital subtraction angiography working view one year follow up with stable complete obliteration, H: postoperative non contrast CT brain axial cut showed the metallic artifact of the coil mass in position of AcomA, I, J: 6 months Postoperative MR angio brain volume rendering reformats and source image axial cut showing successful exclusion of the AcomA aneurysm and clearly reconstructed bifurcation; K: two years Postoperative MR angio brain volume rendering reformats showing stable exclusion of the AcomA aneurysm and clear reconstruction of the bifurcation.

DISCUSSION:
Incidence and prevalence of hypopituitarism after SAH is estimated to be 4.2 per 100,000 per year and 45.5 per 100,000, respectively6, 7, 8. Although its clinical symptoms are usually nonspecific, it can cause life-threatening events and can lead to increased mortality9. The exact mechanism is uncertain and theories put forward are structural hypothalamic pituitary injury, adaptive mechanism to acute illness, raised intracranial pressure, and edema around the hypothalamic-pituitary axis10, 11.

Our study showed that 53.3% of patients with spontaneous SAH suffered from hypopituitarism at baseline. This deficiency persisted in 37% of the patients after 3 months.
Follow up. Recently it has been discovered that the pituitary tissue is capable of regeneration after damage12. This may explain improvement in the pituitary functions in our study. However, due to infarct or structural damage to the hypothalamo-pituitary axis, some hormonal deficiencies may persist and become permanent10.

The prevalence of gonadotrophin and GH deficiency was a more frequent hormonal deficiency in this study. Those patients, who developed a hydrocephalus in the acute phase had high incidence of growth hormone deficiency. There was no correlation between hydrocephalus in the acute stage and the pituitary deficiency at the follow-up. But there was significant correlation between vasospasm and persistent corticotrophic deficiency during follow-up. We found significant relationship between patients who experienced vasospasm in the acute stage and the cortisol levels deficiency at 3 month follow up (p=0.004). But the age of the patients and pituitary dysfunctions had no correlation.

Our findings are quite consistent with many other clinical studies13,14,15,16. Some studies showed that through a screening procedure, neuroendocrine dysfunction was identified in a substantial number of asymptomatic patients with previous SAH. However, some studies have disregarded the myth of chronic hypopituitarism in aneurysmal SAH13.

Aneurysmal or AVM subarachnoid hemorrhage or location of the aneurysm had no significant correlation with the degree of hormonal abnormalities. Moreover, clipping or coiling for aneurysmal cases showed no difference with the degree of improvement of hormonal abnormalities at follow up. We used the Glasgow Outcome Scale to assess the clinical outcome in our patients during follow up and found a significant correlation between pituitary deficiency and poorer GOS scores. Other studies also reported decrease in life satisfaction among patients with pituitary dysfunctions after SAH4. We noticed a significant association between the severity of SAH expressed by Fisher CT scale and low FSH and LH levels in the acute stage which has never been reported before.

When searching the literature related to post-SAH hypopituitarism, conflicting reports are available17. However, all studies showed that SAH is a cause of acute, subacute and chronic hypopituitarism but many studies included traumatic brain injuries with SAH to assess this relationship which casted doubt about the true incidence of hypopituitarism18. Some studies were retrospective and had a lower number of cases which could not meet statistical criteria. In many studies, either selective pituitary hormones were checked or only basal levels of hormones were done. With the advancements of laboratory techniques, it is now clear that many stimulatory tests are required to understand the real concentration of pituitary hormones19. Identification of growth hormone and corticotrophin deficiency generally requires a stimulation test, whereas other deficiencies can be detected by basal hormones in combination with clinical judgment. Some studies performed screening in asymptomatic patients. Short follow up was another drawback of many studies. Only few selected studies had long-term follow up. Many studies included patients of traumatic brain injuries which has well-known association with chronic hypopituitarism20.

Some studies showed that long term survivors of SAH presented with various vague symptoms like fatigue, lethargy and some impairment in their daily activities21. These findings provided a trigger to search for the actual effects of SAH on pituitary functions. It is fact that in the acute stage of SAH, there is real derangement of pituitary functions in terms of low output of various hormones. However, with the passage of time, many pituitary hormones come back to baseline levels. Hypopituitarism prevails in many patients for quite a while. The question that remains still unanswered is whether SAH is a real cause of chronic hypopituitarism or not. So far no solid proof has been found in favor of true chronic hypopituitarism. Optimists are in search of any evidence because hormone replacement therapy can change the real stigma of pituitary insufficiency. Available studies have many confounding factors and biases. Therefore, it is difficult to reach meaningful conclusion.

Our study is also not ideal. It has several limitations. The sample size was small and follow-ups were too short. Moreover, dynamic tests were not done for evaluation of GH and ACTH. This may cause underestimation of the number of patients deficient in these hormones.

Routine neuroendocrine screening for hypopituitarism for all patients would be costly and logistically difficult22. We strongly recommend long term follow up of these patients to recognize clearly whether pituitary hormonal disarray is mere an adaptive response or a permanent sequela23. If hypopituitarism is permanent, the patients may be helped with hormonal replacement therapy6. There is an urgent need for well-designed prospective studies with close collaboration of expert endocrinologists to assess precisely its incidence, prevalence, clinical course and effect on mood.
behavior and quality of life. Lack of awareness of study methodologies are producing very conflicting reports and misguiding the practicing clinicians.

CONCLUSIONS:

Pituitary dysfunction was identified in a substantial portion of patients with subarachnoid hemorrhage, gonadotropins and GH deficiencies persisted over time but no association was found between this dysfunction and poor clinical outcome. Patients with hydrocephalus / vasospasm are at high risk of subsequent hypopituitarism.

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