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# High Prolactin Level as a Predictor of Vasospasm in Aneurysmal Subarachnoidal Hemorrhage

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**Background:** Aneurysmal subarachnoid hemorrhage (aSAH) is a destructive syndrome with a mortality rate of 50%. Recent studies have also suggested a high pervasiveness of hypothalamic-pituitary insufficiency in up to 45% of patients after aSAH. Prolactin has been associated with the pathogenesis of hypertensive irregularities that are linked to pregnancy.

**Material/Methods:** We identified a group of 141 patients with spontaneous SAH due to a ruptured cerebral aneurysm; these patients were operated on at our institution's Neurosurgery and Interventional Radiology Department between 2011 and June 2015. All of the data were obtained retrospectively from medical records.

**Results:** The hormonal abnormalities observed in the initial 24 h after ictus in subjects with subarachnoid SAH were caused by stressful stimulation aggravated by intracranial bleeding.

**Conclusions:** The elevated prolactin levels that occur in patients with aSAH can be used in conjunction with other auxiliary factors that we believe may be beneficial to vasospasm.

**MeSH Keywords:** Prolactin • Subarachnoid Hemorrhage • Vasospasm, Intracranial

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## Background

Aneurysmal subarachnoid hemorrhage (aSAH) is a destructive syndrome with a mortality rate of 50%. In spite of all medical care efforts, 30% of survivors experience perpetual neurological impairment [1]. A considerable factor influencing outcome following treatment of a fractured aneurysm is the neurological condition of the accepted patients, which largely reflects the severity of the hemorrhage. Other risks include recurrent bleeding, initial and secondary vasospasm, and the complexity of the therapeutic intervention [1,2].

Recent studies have also suggested that hypothalamic-pituitary insufficiency is very common following aSAH [3–5]. Hyperprolactinemia (HPRL) is physiological condition that occurs after intercourse and stressful activity, and during lactation and pregnancy. The expected rate of HPRL is 0.4–3% in a healthy population. Prolactin has a crucial role in modulating the immune response [2].

Previous studies have linked dysfunction and subarachnoid hemorrhage (SAH). A number of studies have suggested that endocrine disorders are induced by compression of the hypothalamus-pituitary complex by the aneurysm. Other reported causes are SAH due to perfusion changes, toxins from erupted blood, vasospasm-related ischemia, hydrocephalus, and high intracranial pressure. One additional cause is injury during the surgical procedure [3,4,6,7].

A relationship between prolactin and the pathogenesis of pregnancy-related hypertensive disorders has been reported [8,9]. Reports on the hormone levels in these disorders show they are increased, within normal limits, or decreased [10,11]. There is scant evidence regarding the dominant blood flow and resistance effects of prolactin in intact blood vessels, but reports have associated prolactin with vascular effects. Prolactin as an i.v. infusion has been reported to boost arterial pressure in decerebrate rabbits [12] and to decrease renal blood flow, elevate body fluid level, and increase the pressor response to norepinephrine in rats. The N-terminal 16-kDa particle of prolactin was proved to prevent coronary vessel relaxation of isolated perfused animal hearts. There are also reports of deterioration of endothelial vasodilatory function and insulin susceptibility in subjects with pituitary adenoma and hyperprolactinemia. Prolactin i.v. infusion primarily leads to a decline in blood flow and elevation in coronary vascular resistance, mesenteric, renal, and iliac vascular beds. The structure behind these effects was proven to include beta 2-adrenergic receptor-mediated effects linked to the intracellular NO pathway [13,14].

Pituitary prolactin is a 200-amino acid peptide hormone synthesized in and secreted from the anterior pituitary [9]. Several lines of evidence suggest that prolactin is secreted in the periphery by lymphohematopoietic cells. A number of endogenous and exogenous factors modulate prolactin secretion but, for the purposes of this review, estrogen and dopaminergic agonism are pivotal. Circulating prolactin binds to the prolactin receptor and its various isoforms with specific downstream effects, as would be expected for a receptor that belongs to the growth hormone, erythropoietin, and cytokine receptor superfamily. Signal transduction of the prolactin receptor leads to gene transcriptional regulation. Interestingly, prolactin and the immunosuppressive drug cyclosporine appear to be antagonistic through a receptor-based mechanism.

## Material and Methods

We identified a cohort of 141 patients with spontaneous SAH due to a ruptured cerebral aneurysm; these patients were operated on in Baskent University Neurosurgery and Interventional Radiology Department between September 2011 and June 2015. This study was approved by Baskent University Institutional Review Board (Project no: KA 17/165) and supported by Baskent University Research Fund. All of the data were obtained retrospectively from medical records.

Cerebral angiography was conducted in all patients to determine localization of the aneurysm. All patients that had an SAH underwent brain computed tomography (CT) and results of the CT were noted.

According to the findings of cranial digital subtraction angiography, the localization of the aneurysm, the aneurysm neck diameter, length, and the ratio of the dome and neck length were all recorded. Basal hormone levels of the patients were taken within 12 h of their admission.

Patients that used confounding drugs earlier, such as substituting hormonal therapy of all types, were excluded from this study. Patients using drugs that might affect pituitary function, such as glucocorticoids or dopamine, were additionally excluded. We measured fundamental hormone status along with free (f) T3, fT4, TSH, PRL, cortisol, FSH, LH, and macroprolactin.

We made a diagnosis of spontaneous SAH according to anamnesis, physical findings, and brain CT data. Then, dilatation was detected using four-vessel conventional x-ray angiography (all carotids and all vertebrals) via femoral artery catheterism. When the localization of the aneurysm was visualized, the image of the neck was recorded. The Fisher CT score corresponds to: (1) No blood detected; (2) A diffuse disposition or thin layer with all vertical layers of blood (interhemispheric fissure, insular cistern, ambient cistern) less than 1 mm thick; (3) Localized clots and/or vertical layers of blood 1 mm or more





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in thickness; and (4) Diffuse or no subarachnoid blood, but intracerebral or intraventricular blood [10].

Following hospital admissions, the patients were clinically assessed and categorized in accordance with the World Federation of Neurosurgical Societies (WFNS) SAH grading scale, which is used exclusively in patients with SAH for clinical and predictive assessment. All of the patients were tracked until they were released from the hospital. Prior to release, the patients were re-evaluated using the prognostic WFNS scale [15].

We collected blood samples at 8 AM and 9 AM, 24 h upon ictus, centrifuged at 3000 rpm, for 10 min. We stored the serum at –20° C until we conducted the assays. We measured hormones using commercial kits: T4 by RIA (INEP, Zemun, Serbia); TSH by IRMA (INEP); PRL, LH, and FSH by IRMA (Cis BioInternational, France); and cortisol by RIA (Cis BioInternational).

### Statistical analysis

Statistical analysis was performed using SPSS 20.0.

Normality of distributions of continuous variables was determined by Kolmogorov-Smirnov test. Descriptive statistics for continuous variables are expressed as mean ±SD or median ($25^{th}$–$75^{th}$) percentiles, where applicable. Numbers of cases and percentages were used for categorical data. The mean differences between groups were compared by the *t* test, and Mann-Whitney U test was used for comparisons of non-normally distributed data.

## Results

We identified 141 eligible patients, but 17 patients who were lost to follow-up were excluded. We included 124 patients in the analysis. There were 49 females and 75 males, with an average age of 56.33±11.17 years, and there were no statistically significant differences between the average age of females (52.5±14.8 years) and males (51±3.3 years). Aneurysm location sites are listed in Table 1. Fifty-three subjects were categorized as grade I in the WFNS grading scale (asymptomatic or with minimal to discrete headache), 37 patients were classified as grade II (headache levels moderate to severe, stiff neck, and absence of focal neurological signs, excluding cranial nerves paralysis), and 19 patients were classified as grade III (sleepiness, mental confusion, and discreet focal neurological deficits), 28 patients were classified as grade IV, and 4 patients were classified as grade V.

We assessed endocrine levels at 7.4±6.6 h after SAH. Prolactin levels were significantly correlated with Fischer grade on CT (Pearson correlation coefficient: 0.59, p<0.0001). The mean prolactin levels were 8.23±5.15 (15 patients) in Fischer grade I, 12.93±12.60 (48 patients) in Fischer grade II, 36.08 ± 19.39 (50 patients) in Fischer grade III, and 43.29±24.33 (28 patients) in Fischer grade IV. There were significant differences between prolactin levels with Fischer grades and WFNS grades of the patients (Pearson correlation coefficient 0.496, p<0.0001). The mean prolactin levels were lower for patients with lower Fischer grades (p<0.0001), and there were no differences between prolactin levels and sex (p=0.328). Radiologically, vasospasm was observed in patients with high prolactin levels in diagnostic cerebral angiography, and the aneurysm was closed within 24 h.

**Table 1.** Aneurysm localization of patients.

| | | N | % |
|---|---|---|---|
| 0 | Non anevrizma | 10 | 7.1 |
| 1 | Right ICA | 9 | 6.4 |
| 2 | Right MCA | 16 | 11.3 |
| 3 | Left ANT Com | 41 | 29.1 |
| 4 | Left ICA | 13 | 9.2 |
| 5 | Left MCA | 14 | 9.9 |
| 6 | Right ANT Com | 10 | 7.1 |
| 7 | Post cerebral | 2 | 1.4 |
| 8 | Post Com | 10 | 7.1 |
| 9 | Ant cerebral | 3 | 2.1 |
| 10 | Basiler | 9 | 6.4 |
| 11 | PICA | 3 | 2.1 |
| 12 | Left SCA | 1 | 0.7 |
| | **Total** | **141** | **100.0** |

The TSH, T3, and T4 levels in men and women were comparable. TSH levels were higher than normal in 5 patients (14.2%). T3 levels characterized by a mean value of 33.8±9 ng/dL, were found lower than normal in 5 patients (14.2%). The T4 levels were low in 2 patients (5.6%). Antithyroglobulin and antimicrosomal antibodies were not identified in any of the subjects.

We divided the patients according to their aneurysmal site, in terms of anterior circulation and posterior circulation. There were 83 anterior circulation aneurysm patients and 41 posterior circulation aneurysm patients. The mean prolactin levels were 29.98±23.43 and 16.31±15.42 in anterior and posterior circulation aneurysms, respectively. We found significant differences between aneurysmal site and prolactin levels (p=0.001). There were no differences in aneurysm site between aneurysm neck diameter, dome length/neck size ratio, and Fischer and WFNS grades. Radiologic vasospasm detected in diagnostically





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**Table 2.** Prolactine and cortisol level.

| | Cortisol | | |
|---|---|---|---|
| | r | P | n |
| Prolactine | .784** | .000* | 141 |

* p<0.05. There were statistically significant positive relationship between prolactin and cortisol (p<0.05). As prolactin increases, cortisol increases.

constructed cerebral angiographies was observed in Fischer grade and WFNS grades with high prolactin levels. There was a statistically significant positive correlation between prolactin and cortisol (p<0.05) (Table 2). There was a statistically significant positive correlation between prolactin, cortisol, and Fischer grade, D/N ratio, and size (mm) (p<0.05). Fischer grade, D/N, and cortisol increased as size increased (Table 3).

## Discussion

The pathophysiology of neuroendocrine dysfunction upon SAH is obscure. It has been suggested that the genesis of these adjustments may be the ischemic or hemorrhagic lesions in the hypothalamus or pituitary gland. Increased intracranial pressure, local tissue pressure changes upon hemorrhage, vasospasm-based ischemia, microinfarctions of the pituitary gland, venous stasis, and surgical procedures may damage the pituitary gland [3]. The pathogenesis of aSAH [10,15–18] can also include traumatic brain injuries, genetic predisposition, and autoimmunity and neuroinflammatory responses. Insufficiencies in all pituitary hormones following SAH have been reported to differ from none to 68% in previous studies [5,11,17,19]. Our results revealed increased prolactin levels beginning 12 h after SAH.

The increase in cortisol during stress is a necessary mechanism for the defense of the human body in the perpetuation of its homeostasis. Alterations of the excitability of the neuronal membranes [20] can be immediately activated by glucocorticoids. Cerebrovascular permeability and the choroidal transport of water and electrolytes may also be affected, and they are crucial for the regulation of liquor synthesis and volume homeostasis in the brain [19]. Complicated intercommunication between the immune system and the hypothalamus-pituitary-adrenal axis can also be of crucial physiological significance in the stress response [20]. Glucocorticoids produce a multistep restriction of the immune system that protects against the aftereffects of extreme inflammatory reactions [20,21]. Our study also revealed that higher levels of cortisol were correlated with higher Fisher grades.

**Table 3.** Relationship between prolactine levels and other variables.

| | Prolactine | | |
|---|---|---|---|
| | r | P | n |
| Fischer grade | .502** | .000* | 141 |
| Age | .106 | .210 | 141 |
| D/N | .189* | .025* | 141 |
| Size (mm) | .126 | .135 | 141 |

* p<0.05. The correlation between prolactin levels, Fisher grade and D/N ratio were statistically significant (p<0.05). As Fisher grade increased, prolactin levels also rised. There was no statistically significant relationship between age and size of the aneurysm (p>0.05).

It has been shown that prolactin IV infusion mainly causes a decline in blood flow and elevates vascular protection in the coronary, mesenteric, renal, and iliac vascular beds. The structures of these reactions have been proven to include beta 2-adrenergic receptor-mediated reactions that are connected with the intracellular NO pathway [13].

The decline in the tracked blood flow against prolactin IV infusion might be related to a main reaction of the hormone and not to concomitant alterations in hemodynamic variables. The heart rate and arterial blood pressure of the patients were kept consistent, and there were no important alterations in heart filling pressures and left ventricular dP/dtmax. This case prohibited any secondary intervention from reflexes, local metabolic, or natural effects on the reaction of tracked blood flows to prolactin immersion. Moreover, IV immersion of the vehicle only at the identical rate with prolactin did not result in the same reactions of the immersed hormone. Also, the candid connection between the hormone and its coronary, mesenteric, renal, and iliac reactions was validated in the dose-response study, which proved that the increase in regional blood flow could be developed by enhancing the dosage amount of the immersed hormone. Several lines of evidence suggest that prolactin is secreted peripherally by lymphohematopoietic cells [12]. The role of prolactin in lymphoproliferation and its effects on cytokine production are also important. Prolactin acts through potentiation of T and B cell function [22].

Henderson et al. showed that the coronary, mesenteric, renal, and iliac vasoconstriction caused by prolactin immersion contained both the endothelial discharge of NO and its intracellular direction. Although we did not measure the real discharge of NO, the regional vasoconstriction drawn out by hormone infusion was counteracted by the local intra-arterial administration of L-NAME, which has been proven to prevent the formation of NO [21].





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In our analysis, patients who presented a more severe clinical status on upon WFNS evaluations and greater bleeding on CT (Fisher grade) exhibited a higher propensity for endocrinological disorders. Klose et al. [23] observed a correlation between lower GCS and the presence of hydrocephalus with hormonal changes in the first days after SAH.

In patients with SAH, delayed cerebral ischemia with arterial vasospasm can be an important cause of disability and death. In our treatment protocol, we used the previous version of these guidelines, which focused on prevention with oral nimodipine and maintenance of euvolemia, as well as treatment with triple-H and endovascular therapy with selective intra-arterial vasodilators and/or balloon angioplasty [24]. We also treated the patients with acute hydrocephalus by external ventricular drainage (EVD) and/or lumbar drainage.

Mangieri et al. [21] studied the hormonal profiles of patients in the hyperacute phase of SAH (the first 24 h). These authors observed an increase in cortisol in all patients studied (n=35), a finding that was most likely due to the physiological response to stress. Mangieri et al. also observed a higher incidence of high prolactin (14.2%). In terms of thyroid hormones, these authors observed high levels of TSH in 14.2% of patients, low levels T3 in 14.2% of patients, and low levels of T4 in 5.6% of patients; FSH and LH were unaffected [21]. In our study, we found high prolactin and cortisol levels in early-stage SAH. Nakagava et al. [25] described the clinical features of cerebral blood flow (CBF) data obtained from single-photon emission computed tomography (SPECT) during the risk period for DCI after SAH. We performed cerebral angioplasty and/or selective intra-arterial vasodilator therapy in the region of hypoperfusion of arterial territories after SPECT in the patients with high GCS and neurological regression.

## Conclusions

Early detection of vasospasm may prevent morbidity and mortality after aneurysm rupture, and it improve outcomes. On the contrary, better selection of patients prevents complications of aggressive treatment such as induced hypertension and hypervolemia, as well as interventional therapies. Elevated prolactin levels have a potentially valuable role in identifying SAH patients at higher risk of developing vasospasm beyond Fischer and WFNS scales. Future studies of related mechanism of prolactin secretion in SAH patients may also identify new targets of treatment.

### Conflicts of interest

None.

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