

# Endocrine Function Following Acute SAH

Paul Vespa · The Participants in the International Multi-disciplinary  
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**Abstract** Disruption of the hypothalamic–pituitary–adrenal axes may occur after aneurysmal subarachnoid hemorrhage, resulting in hypopituitarism. An electronic literature search was conducted to identify articles with English-language abstracts published between 1980 and March 2011, which addressed hypothalamic–pituitary–adrenal axis insufficiency and hormone replacement. A total of 18 observational and prospective, randomized studies were selected for this review. Limited data are available, evaluating pituitary effects during the acute stage after subarachnoid hemorrhage, with inconsistent results being reported. Overall, after acute subarachnoid hemorrhage, cortisol levels may initially be supranormal, decreasing toward normal levels over time. During the months to years after subarachnoid hemorrhage, pituitary deficiency may occur in one out of three patients. Limited data suggest modest outcome benefits with fludrocortisone and no benefit or harm from corticosteroids.

**Keywords** Adrenal insufficiency · Adrenocorticotrophic hormone · Cortisol · Growth hormone · Hypothalamic

## Introduction

Aneurysmal subarachnoid hemorrhage (SAH) presents with widespread medical complications that include disruption of the hypothalamic–pituitary–adrenal (HPA) axis. Sodium imbalance in SAH related to the syndrome of inappropriate antidiuretic hormone secretion or cerebral salt wasting syndrome is addressed elsewhere (see Chapter Hyponatremia). Hypopituitarism may occur following brain injury, including after SAH [1–3]. An initial surge in the sympathetic nervous system is associated with the release of catecholamines and cortisol. Dysfunction of the HPA can result in acute physiological problems in the critical care setting and potentially in long-lasting effects on cognitive outcome after SAH [4, 5].

This study was designed to evaluate the incidence and consequences of HPA insufficiency in patients with SAH. The literature was also reviewed for investigating whether acute hormonal replacement therapy is beneficial for the SAH patient, including the use of corticosteroids for the purpose of enhancing hemodynamic and cognitive outcomes.

## Methods

An electronic literature search was performed by conducting a PubMed survey for articles published from 1980 to March 2011. Candidate articles were identified using the keywords “subarachnoid hemorrhage,” “pituitary,” “hypothalamus,” “corticosteroids,” “adrenal insufficiency,” “outcomes,”

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and “mortality.” Titles and abstracts from initially identified citations were reviewed for relevance to the topic of pituitary dysfunction in patients with aneurysmal SAH and study design. Articles were included if they described original research involving human subjects and were designed as observational or randomized trials and the abstract was available in English. Selected studies were evaluated using the GRADE system for quality [6].

### Summary of the Literature

A total of 206 articles were initially identified as potential candidate articles. From these, 38 original research studies were identified, with 18 observational and prospective, randomized studies being selected for this review.

#### Incidence of HPA Insufficiency

Several prospective observational studies have been performed to document the incidence of dysfunction of the

HPA axes, primarily through prospective measures of individual hormonal concentrations in the acute and chronic setting (Table 1 [4, 7–16]). Unfortunately, most studies focus on the chronic setting from 12 to 72 months after SAH. In the chronic setting, the prevalence of a cortisol deficiency ranges from 2.5 to 40% of patients. Another study showed endocrine dysfunction in nearly half of the 30 patients evaluated 12–24 months after SAH (47%), with cortisol hyporesponsiveness to the low-dose corticotropin stimulation test in 10% [17]. A small study sampling 14 patients after SAH and 15 matched controls identified sympathetic activation with 3–4 times increased norepinephrine spillover to plasma, 2–7 days after SAH [18].

Six studies evaluated the HPA in acute SAH [7, 9–11, 13, 16]. Deficiencies in adrenocorticotrophic hormone (ACTH) and stimulation-induced elevation in cortisol were found in acute SAH by Kelly and colleagues [7] and Dimopoulou and colleagues [10], whereas normal cortisol was found by Savaridas. Bendel et al. [11] documented that ACTH and cortisol values were higher in the acute SAH

**Table 1** HPA disorders after SAH

Study	Time after SAH	HPA abnormality	Impact on outcome	GRADE criteria
Kelly et al. [7]	Acute	Pituitary deficiency: TRH, ACTH	Outcome not studied	Low—too small ( <i>n</i> = 2)
Kreitschmann-Andermahr et al. [8]	12–60 months	Pituitary deficiency: ACTH, GH	Outcome not studied	Low—chronic
Savaridas et al. [9]	Acute	Normal ACTH, cortisol levels	Outcome not studied	Low—too small ( <i>n</i> = 6)
Kreitschmann-Andermahr et al. [4]	12–72 months	Pituitary deficiency: ACTH, TRH, GH	No effect on outcome	Moderate—chronic
Dimopoulou et al. [10]	Acute	Pituitary deficiency: ACTH, deficient stimulation of cortisol	Worse outcome in relative adrenal insufficiency	Low—acute
Bendel et al. [11]	Acute followed by chronic	Supranormal ACTH and cortisol	No effect on outcome; normalization ACTH and cortisol by 3 months	Moderate—acute
Aimaretti et al. [12]	12–60 months	Pituitary deficiency: ACTH, GH	No effect on outcome	Low—acute
Weant et al. [13]	Acute	Relative adrenal insufficiency in pressor unresponsive patients only	Outcome not studied	Moderate—acute
Srinivasan et al. [14]	5–12 months	Pituitary deficiency: GH; adrenal insufficiency	Effect on functional outcome using 18-item Functional Independence Measure score	Moderate—chronic
Lammert et al. [15]	3–6 months	Pituitary deficiency varied, but low prevalence overall	No effect on outcome	Moderate—chronic
Poll et al. [16]	Acute	Supranormal to normal cortisol levels; no low levels found. Variable ACTH levels; abnormal diurnal variation	No effect on outcome	Moderate—acute

ACTH adrenocorticotrophic hormone, GH growth hormone, TRH thyrotropin-releasing hormone

patients than in age-matched controls. The degree of cortisol elevation was not associated with the severity of SAH. In contrast, mixed results of normal cortisol with low or normal levels of ACTH were found by Poll et al. [16]. In the latter study, the diurnal variation of free cortisol levels was abnormal in some SAH patients, and correlated with poor outcome and longer length of stay compared with those patients with normal diurnal variation. High levels of cortisol have recently been associated with delayed cerebral ischemia, although the causality of this observation is unclear [19]. Overall, there is a paucity of evidence that significant HPA dysfunction occurs in the acute phase of illness in most SAH patients. Most studies either did not study the effect of HPA dysfunction on outcome or could find no specific effect on outcome.

In contrast, a recent study of a particular subgroup of SAH patients who exhibit vasopressor-resistant hypotension suggests that relative adrenal insufficiency may occur [13]. In the latter observational, convenience sample study, 18% of SAH patients were found to have vasopressor-resistant blood pressures during the induction of hypertensive therapy. In that subgroup, 69% were found to have relative adrenal insufficiency, as defined by a positive response to the cosyntropin stimulation test. This latter study suggests that there may be an important subgroup of patients with relative adrenal insufficiency requiring hormonal replacement therapy with hydrocortisone to assist with inducing therapeutic hypertensive therapy.

### Hormonal Replacement Therapy for SAH

There are very few prospective studies, evaluating the influence of hormonal replacement therapy on SAH. There have been two prospective studies on the use of fludrocortisone [20, 21], one on hydrocortisone [22], and one on methylprednisolone [23]. Treatment with fludrocortisone was weakly associated with decreased delayed cerebral ischemia (RR 0.65; 95% CI 0.33–1.27) and lower mortality (RR 0.33; 95% CI 0.03–3.20). The wide confidence intervals highlight the modest effects of this treatment. Mineralocorticoids are frequently used in the treatment of hyponatremia, which is discussed in the Hyponatremia Chapter.

The use of corticosteroids has been sparsely studied as well. In the single trial of hydrocortisone, there was an increased one-month mortality rate (RR 1.49; 95% CI 0.85–2.61) and higher incidence of hyperglycemia [23 as discussed in 25]. The recent study by Gomis et al. [23] was a single-center, randomized, controlled trial of high-dose methylprednisolone (18 mg/kg/day for 3 days) in 95 patients with SAH. In this study, patients exposed to methylprednisolone experienced a similar incidence of key outcome variables as compared with the placebo group, including symptomatic vasospasm (28 vs 31.5%,  $P < 0.7$ ),

modified Rankin Scores at 12 months ( $P < 0.08$ ), delayed ischemic neurologic deficits on imaging (24.4 vs 18.4%,  $P < 0.8$ ), and death (18.3 vs 17.3%,  $P < 0.8$ ). Gomis et al. highlight that functional outcome, determined using a modified version of the Rankin Scores, which excludes all patient deaths, was better in the methylprednisolone group. This form of analysis is unprecedented in similar outcome trials, and hence, the conclusions based on this analysis cannot be taken at face value. In summary, the existing data suggest that effect of corticosteroid replacement ranges from harmful to no benefit in outcome [24].

### Conclusions

In acute SAH, there is a disruption of the diurnal variation of the HPA, with initially supranormal cortisol levels that decrease to normal or near-normal concentrations over time. During the chronic period lasting months to years after SAH, a deficiency in pituitary function appears to exist in one-fourth to one-third of patients. The replacement of mineralocorticoid function using fludrocortisone may convey a weak beneficial effect at best. Corticosteroids replacement using hydrocortisone or methylprednisolone may be harmful or, at best, ineffective.

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