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Neuroendocrine changes after aneurysmal subarachnoid haemorrhage

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Abstract

Introduction The prevalence of pituitary dysfunction is high following aneurysmal subarachnoid hemorrhage (aSAH) and when occurs it may contribute to residual symptoms of aSAH such as decreased cognition and quality of life. Hypopituitarism following aSAH may have non-specific, subtle symptoms and potentially serious consequences if remained undiagnosed.

Methods We reviewed the literature on epidemiology, pathophysiology, diagnostic methods and management of neuroendocrine changes after aSAH as well as on the impact of pituitary dysfunction on outcome of the patient.

Results The prevalence rates of pituitary dysfunction after aSAH varies greatly across studies due to different diagnostic methods, though growth hormone deficiency is generally the most frequently reported followed by adrenocorticotropic hormone, gonadotropin and thyroid stimulating hormone deficiencies. Pituitary deficiency tends to improve over time after aSAH but new onset deficiencies in chronic phase may also occur. There are no clinical parameters to predict the presence of hypopituitarism after aSAH. Age of the patient and surgical procedures are risk factors associated with development of hypopituitarism but the effect of pituitary dysfunction on outcome of the patient is not clear. Replacement of hypocortisolemia and hypothyroidism is essential but treatment of other hormonal insufficiencies should be individualized.

Conclusions Hypopituitarism following aSAH necessitates screening despite lack of gold standard evaluation tests and cut-off values in the follow up, because missed diagnosis may lead to untoward consequences.

Keywords Aneurysmal subarachnoid haemorrhage · Hypopituitarism · Neuroendocrine dysfunction · Diabetes insipidus

Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) occurs with an incidence of 6–10/100,000 per year [1] with an age predilection of 40–60 years. The 6-months mortality rate is about 50%. The progress in neurosurgical, endovascular and neurointensive care unit facilities led to an increase in the number of survivors of patients with aSAH [2]. However, aSAH has major social, functional and economic implications since it affects patients in their most reproductive years.

Neuroendocrine dysfunction may be one of the contributing factors for residual symptoms after aSAH such as decreased cognition and quality of life [3–5]. In a recent meta-analysis, the prevalence of pituitary dysfunction was found to be high suggesting the necessity for screening protocols for both acute and long-term follow-up to select patients requiring more detailed investigation [6].

The cognitive and functional deficits observed after aSAH resemble to the non-specific symptoms of hypopituitarism which might be missed easily and might have serious, sometimes life threatening consequences in affected patients.

Epidemiology of pituitary dysfunction in aSAH

Symptomatic hypopituitarism was first reported as a late complication of aSAH in three cases in 1961 [7]. The first structured study in 1969 showed abnormal diurnal variation of plasma cortisol in 65% and subnormal urinary steroid response after metyrapone in 44% of cases with aSAH [8]. There is considerable variation in later studies evaluating the prevalence of pituitary dysfunction after aSAH.

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Hypopituitarism affecting at least one of the pituitary axis after aSAH was reported at rates of 37–55% [3, 5, 9–11]. The pooled prevalence of hypopituitarism in general was found to be 47% (95% confidence interval = 37–57%) in an early metaanalysis [12]. Table 1 summarizes the studies showing the prevalence of pituitary dysfunction in patients with aSAH (Table 1).

Most studies consistently show relative preponderance of growth hormone (GH) deficiency (GHD) after aSAH followed by adrenocorticotropic hormone (ACTH), gonadotropin and thyroid stimulating hormone (TSH) deficiency [30, 33, 34]. In the acute phase of aSAH, gonadotropin levels are usually low which recover in the long term follow-up. A mild degree of hyperprolactinemia may also be seen that resolve in a few months time [5]. Kopczak et al. investigated 509 patients with brain injury (169 of them with aSAH) in a neurorehabilitation center < 1 month after the event. Among aSAH patients 30.1% of men without concomitant hyperprolactinemia showed decreased testosterone values. Hypogonadism was detected in 19.1% of all men (T < 230 ng/dL) [25]. However, the study was designed to test the efficiency of a screening program, therefore no confirmatory tests were performed.

In a recent metaanalysis, the time point of evaluation was demonstrated to influence the frequency of pituitary dysfunction after aSAH. The prevalence of any type of hypopituitarism was shown to decrease over time, ranging from 31% (95% CI 0.22–0.43) at 3–6 months to 25% (95% CI 0.16–0.36) at 6 months [33]. A trend of improvement in hypogonadotropic hypogonadism, diabetes insipidus, and multiple hormone deficiencies by time, which was statistically not significant was reported. The prevalence of secondary adrenal insufficiency and secondary hypothyroidism remained unchanged and GHD persisted in the long-term with an increasing trend of deterioration [33]. A prospective study of 100 aSAH patients revealed 14% of hypocortisolism in the acute setting according to basal cortisol levels. However only 5% had ACTH deficiency and 10% GHD with dynamic testing in the long-term [35].

Robba et al. in their metaanalysis defined the acute phase of the aSAH as the first 6 months after the event and the chronic phase as the period after 6 months [6]. Overall prevalence of altered basal hormone levels was found to be 36.4% (95% CI 23.7–51.3). The pooled prevalence of abnormal stimulation tests were 29% (95% CI 18.7–42.2). The prevalence of pituitary dysfunction in the acute phase was 49.3% (95% CI 41.6–56.9) and 25.6% (95% CI 18.0–35.1) in the chronic phase. Single pituitary hormone dysregulation in total was found to be much higher than multiple pituitary hormone deficiencies.

The results showing prevalences of pituitary dysfunction in three metaanalyses were compatible with each other. Nearly half of the patients in the early phase of aSAH and a quarter of patients in the chronic phase harbor pituitary dysfunction [6, 12, 33]. These metaanalyses share the limitations of original studies and there is a high heterogeneity in the prevalence rates. The heterogenous results in the studies can be explained by time points and methods of assessment, inclusion and exclusion criteria and management method of aneurysm applied. Although there is a trend of improvement in pituitary dysfunction by time [6], some studies have shown new onset deficiencies in the chronic phase of aSAH also [20, 22, 30, 36].

An important factor affecting the prevalence of hormone deficiency is the diagnostic method and cut-offs used to assess the pituitary functions. Somatotrophic axis has been evaluated by serum IGF-1 in some studies [5, 16, 20], GHRH-arginine test in some [3, 10, 14, 17, 27], insulin tolerance test (ITT) [13, 17, 26, 35] or glucagon stimulation test (GST) [22, 35, 37]. The detected rate of GHD was the highest with GHRH-arginine test among all tests (25%). Studies that used higher cut-off levels (< 9 µg/L) of GH led to higher prevalence of GHD than studies which used lower cut-off levels (< 8 µg/L). The reported frequency of GHD was lowest with ITT (15%) (cut-off level used was 3 µg/L in all studies). For the GST cut-offs used were 1.18 µg/L and 3 µg/L for GHD and reported pooled frequency was 23% [9].

Hypothalamic-pituitary-adrenal (HPA) axis was evaluated by basal cortisol level [9, 10, 21], ACTH stimulation test (low [5] and standard dose [17, 27, 35]) and GST [3, 35, 37]. The pooled prevalence of adrenal insufficiency was lowest (5%) with basal cortisol measurement, 10% with ACTH test, 16% with ITT and highest (22%) with GST. Cut-offs used directly affected the frequencies, when higher cut-offs were used frequency of adrenal insufficiency increased and when lower cut-offs were used frequency of adrenal insufficiency decreased [9].

Secondary hypothyroidism was usually evaluated with free thyroxine and TSH levels, TRH stimulation test and T3 resin uptake was used in only one study [17]. The pooled prevalence of secondary hypothyroidism was 4% [9].

Hypogonadotropic hypogonadism had a pooled frequency of 11% [9]. Prolactin levels were found to be low in general, however mild hyperprolactinemia was seen in some of the studies (Table 1).

Hypopituitarism seems to be a common complication of hypopituitarism. The reported prevalence rates vary considerably due to different dynamic tests and cut-offs used in the studies. However, due to potentially harmful consequences of missed diagnosis of hypopituitarism, screening should be carried out despite lack of gold standard evaluation tests and cut-off values.

Table 1 Studies showing the prevalence of pituitary dysfunction in patients with aSAH

First author, year of publishing	Study design	Evaluation time following aSAH	Pituitary dysfunction and impaired axes	Hormonal evaluation methods	Predictors of pituitary dysfunction
Kreitschmann-Andermahr 2004 [13]	Cross-sectional n = 40 (14 men) Mean age: 43.8 years	12–66 months (27.3 months, mean)	Pituitary dysfunction 55% GH insufficiency 20% ACTH insufficiency 40% TSH insufficiency 2.5% FSH/LH insufficiency 0% Hyperprolactinemia 10% DI 0%	*Baseline hormone concentrations* (TSH, fT4, fT3, LH, FSH, total testosterone (in males), estradiol (in females), prolactin, cortisol, ACTH, IGF-I) *ITT* (peak cortisol < 18.1 µg/dL; severe GHD: peak GH < 3 µg/L; partial GHD: peak GH ≥ 3 µg/L and < 5 µg/L) *TRH-LHRH-arginine test*	Female gender and premature rupture of aneurysm (intraoperative rupture before neck was secured) was associated with cortisol deficiency Vasospasm was less frequent in patients with GHD
Dimopoulou 2004 [5]	Cross-sectional n = 30 (14 men) Mean age: 50 years	12–24 months	Pituitary dysfunction 47% GH insufficiency 37% ACTH insufficiency 10% FSH/LH insufficiency 13% Hyperprolactinemia 23%	*Baseline hormone concentrations* (TSH, fT4, T3, LH, FSH, testosterone(in males), estradiol (in females), prolactin, DHEAS, cortisol, ACTH, GH, IGF-1) *ACTH stimulation test* (1 µg) (peak cortisol < 18 µg/dL)	No correlation was found between severity of aSAH and later PD
Aimaretti 2005 [14]	Prospective n = 32 (12 men) Mean age: 51.9 years	3rd month (n = 32)	Pituitary dysfunction 46.8% (3rd month) GH insufficiency 25% ACTH insufficiency 3.1% FSH/LH insufficiency 9.3% TSH insufficiency 9.3% Hyperprolactinemia 3.1% DI 6.25%	*Baseline hormone concentrations* (TSH, fT4, LH, FSH, testosterone(in males), 17βE2 (in females), prolactin, cortisol, 24-h urinary free cortisol, IGF-1, diuresis, urine density, Na, plasma osmolality) *GHRH-arginine test*[1] (peak GH < 9 µg/L)	Fisher score was not related to PD or peak GH after GHRH-arginine test
		12th month (n = 32)	Pituitary dysfunction 37.5% (12th month) GH insufficiency 21.8% ACTH insufficiency 6.25% FSH/LH insufficiency 6.25% TSH insufficiency 9.3% Hyperprolactinemia 3.1% DI 2.8%		
Bendel 2008 [4]	Prospective n = 30 (14 men) Mean age: 52 years (Control group, n = 16)	1–7 days (n = 30)	ACTH insufficiency 33% (1–7 days)	*Baseline hormone concentrations* (serum free and total cortisol, CBG, albumin, ACTH, 24-h urinary cortisol)	Patients with aSAH had higher total and free cortisol at first evaluation but not at 3rd month
		3rd month (n = 26)	ACTH insufficiency 3.8% (3rd month)	*ACTH stimulation test* (250 µg) (peak cortisol < 8.9 µg/dL)	Severity of aSAH did not affect total and free cortisol concentrations

Table 1 (continued)

First author, year of publishing	Study design	Evaluation time following aSAH	Pituitary dysfunction and impaired axes	Hormonal evaluation methods	Predictors of pituitary dysfunction
Tanriverdi 2008 [3]	Prospective n = 22 (11 men) Mean age: 47.9 years	First 24 h (n = 22)	Pituitary dysfunction 63,6% (first 24 h) GH insufficiency 22.7% ACTH insufficiency 22.7% FSH/LH insufficiency 31.8% TSH insufficiency 0% Hyperprolactinemia 22.7%	*Baseline hormone concentrations* (TSH, fT4, fT3, LH, FSH, total and free testosterone (in males), estradiol (in females), prolactin, cortisol, ACTH, IGF-I, GH)	Clinical grade on admission and severity of bleeding was not related to PD PD recovered in 68.2% of patients New-onset PD developed in 40.9% of patients
		12th month (n = 22)	Pituitary dysfunction NA (12th month) GH insufficiency 36.4% ACTH insufficiency 13.6% FSH/LH insufficiency 0% TSH insufficiency 0% Hyperprolactinemia 0%	*GHRH-arginine test* (peak GH < 9 µg/L) *Glucagon stimulation test* (peak cortisol < 10.9 µg/dL)	
Weant 2008 [15]	Retrospective n = 16 (2 men) Mean age: 57.8 years	5.5 days (median)	ACTH insufficiency 68.8%	*Baseline hormone concentrations* (cortisol) *ACTH stimulation test* (1 µg) (relative adrenal insufficiency was defined as baseline cortisol < 15 µg/dL or change in cortisol level < 9 µg/dL after stimulation test)	NA
Jovanovic 2010 [16]	Cross-sectional n = 93 (30 men) Mean age: 48 years	1.8 year (mean)	Pituitary dysfunction 49.4% GH insufficiency 29% ACTH insufficiency 21.5% FSH/LH insufficiency 7.5% TSH insufficiency 4.3% Hyperprolactinemia 4.3% DI 0%	*Baseline hormone concentrations* (TSH, fT4, LH, FSH, total testosterone (in males), estradiol (in females), prolactin, cortisol, IGF-I)	Presence of vasospasm, hydrocephalus during acute phase was related to PD ICA aneurysms were associated with lower IGF-1 levels Vertebrobasilar aneurysms were associated with lower total testosterone
Klose 2010 [17]	Cross-sectional n = 62 (14 men) Median age: 49 years (Control group, n = 30)	7 days(median) (n = 26)	Pituitary dysfunction 58% (7 days) GH insufficiency 15% ACTH insufficiency 12% FSH/LH insufficiency 58% TSH insufficiency 0%	*Baseline hormone concentrations* (TSH, TT4, fT4,fT3, LH, FSH, total testosterone (in males), estradiol (in females), prolactin,total cortisol, IGF-I, GH, IGFBP-3)	Early PD was associated with lower GCS and hydrocephalus but not with H&H or FS
		14 months (median) (n = 62)	None of the patients had PD (14 months)	*ACTH stimulation test* (250 µg) (30 min cortisol < 18 µg/dL) *GH-arginine test*[1] *ITT* (peak cortisol < 18 µg/dL, peak GH < 3 µg/L)	
Poll 2010 [18]	Prospective observational n = 22 (8 men) Mean age: 47.2 years	At admission 7.5 days (mean) 17.1 days (mean)	Diurnal variation evaluated Abnormality: 45% (7.5-days evaluation) 50% (17.1-days evaluation)	*Baseline hormone concentrations* (cortisol, CBG, ACTH) *Diurnal cortisol, CBG* (at 8th, 12th, 16th, 20th hours), calculated free serum cortisol	H&H and FS were not associated with morning or evening values of calculated free serum cortisol at 7.5 day or 17.1 days of evaluation

Table 1 (continued)

First author, year of publishing	Study design	Evaluation time following aSAH	Pituitary dysfunction and impaired axes	Hormonal evaluation methods	Predictors of pituitary dysfunction
Lammert 2011 [19]	Prospective n = 26 (6 men) Mean age: 49 years	3rd month (n = 26)	Pituitary dysfunction 23% (3rd month) GH insufficiency 0% ACTH insufficiency 3.8% (Sufficient response with ITT but not with ACTH stimulation test) FSH/LH insufficiency 7.7% TSH insufficiency 3.8% Hyperprolactinemia 3.8%	*Baseline hormone concentrations* (TSH, fT4,T3, LH, FSH, testosterone (in males), estradiol (in females), SHBG, prolactin, cortisol, ACTH, IGF-I, GH)	NA
		6th month (n = 22)	Pituitary dysfunction 11.5% (6th month) GH insufficiency 0% ACTH insufficiency 4.5% (Sufficient response with ITT but not with ACTH stimulation test) FSH/LH insufficiency 0% TSH insufficiency 4.5% Hyperprolactinemia 3.8%	*ACTH stimulation test* (250 µg) (peak cortisol at 30 min < 18 µg/dL) *ITT* (peak cortisol < 18 µg/dL, peak GH < 3 ng/mL)	
Lammert 2012 [20]		12 months	Pituitary dysfunction 0% (5 patients had low IGF-1 but normal ITT)		
Dutta 2012 [21]	Retrospective and prospective n = 60 (37 men) Mean age: 44.9 years	At ictus (n = 13)	Pituitary dysfunction NA (at ictus) GH insufficiency 53.8% FSH/LH insufficiency 61.5% TSH insufficiency 23% DI 7.7%	*Baseline hormone concentrations* (TSH, T4, LH, FSH, testosterone (in males), estradiol (in females), prolactin, cortisol, IGF-I)	H&H and FS were not related to PD
		6th month (n = 60)	Pituitary dysfunction 31.6% (6th month) GH insufficiency 8.3% FSH/LH insufficiency 6.6% TSH insufficiency 1.6% DI 0%		
Karaca 2013 [22]	Prospective n = 20 (12 men) Mean age: 47.6 years	3rd year	Pituitary dysfunction 20% GH insufficiency 20% ACTH insufficiency 0% FSH/LH insufficiency 0% TSH insufficiency 0%	*Baseline hormone concentrations* (TSH, fT4, fT3, LH, FSH, total and free testosterone (in males), estradiol (in females), prolactin, cortisol, ACTH, IGF-I) *Glucagon stimulation test* (peak cortisol < 10.7 µg/dL, peak GH < 1.18 µg/L)	NA
Lanterna 2013 [23]	Prospective n = 26 (7 men) Mean age: 53.5 years	1–15 days	ACTH insufficiency 42.3%	*Baseline hormone concentrations* (cortisol) *ACTH stimulation test* (1 µg) (change in cortisol < 9 µg/dL)	NA

Table 1 (continued)

First author, year of publishing	Study design	Evaluation time following aSAH	Pituitary dysfunction and impaired axes	Hormonal evaluation methods	Predictors of pituitary dysfunction
Pereira 2013 [24]	Cross-sectional n = 66 (22 men) Mean age: 48.3 years	7.4 days (mean)	Pituitary dysfunction 59.1% GH insufficiency 28.7% ACTH insufficiency 18.1% FSH/LH insufficiency 34.8% TSH insufficiency 9%	*Baseline hormone concentrations* (TSH, fT4, T3, LH, FSH, total and free testosterone (in males), estradiol (in females), prolactin, cortisol, ACTH, IGF-I, GH)	GCS, H&H and FS were related to PD
Kopczak 2014 [25]	Cross-sectional n = 169 (67 men) Mean age: 49 years	7th week (median)	Insufficiency in; one axis 23.7% ≥ 2 axes 2.4% (no detailed data on each axis)	*Baseline hormone concentrations* (TSH, fT4, testosterone (in males), estradiol (in females), prolactin, cortisol, IGF-I) *ACTH stimulation test* (250 µg) (peak cortisol < 18 µg/dL) *GHRH-arginine test*[1] *ITT* (peak cortisol < 18 µg/dL, peak GH < 3 mg/L)	NA (Results were reported in combination with TBI patients.)
Kronvall 2014 [26]	Prospective n = 51 (8 men) Median age: 55 years	5–10 days (n = 51)	Pituitary dysfunction 37% (5–10 days) GH insufficiency 12% ACTH insufficiency 8% FSH/LH insufficiency 30% TSH insufficiency 6% DI 0%	*Baseline hormone concentrations* (TSH, fT4, testosterone (in males), LH, FSH, estradiol (in females), SHBG, prolactin, cortisol, ACTH, IGF-I, GH, Na, serum and urine osmolality)	PD during acute phase was more common in patients with bleeding close to hypothalamus (circle of Willis) and in patients treated by coiling
		3–6 months (n = 45)	Pituitary dysfunction 27%(3–6 months) GH insufficiency 7% ACTH insufficiency 18% FSH/LH insufficiency 4% TSH insufficiency 2% DI 0%	*GHRH-arginine test*[1]	GHD at 3–6 months was more common in younger patients
Kronvall 2015 [27]		6–12 months (n = 44)	Pituitary dysfunction 34% (6–12 months) GH insufficiency 20% ACTH insufficiency 20% FSH/LH insufficiency 2% TSH insufficiency 0%	*Baseline hormone concentrations* (TSH, fT4, testosterone (in males), LH, FSH, estradiol (in females), SHBG, prolactin, cortisol, ACTH, IGF-I, GH, Na, serum and urine osmolality)	Severity, localization, type of treatment was not related to PD
		12–24 months (n = 44)	Pituitary dysfunction 43% (12–24 months) GH insufficiency 25% ACTH insufficiency 20% FSH/LH insufficiency 11% TSH insufficiency 0%	*ACTH stimulation test*(250 µg) (peak cortisol < 20 µg/dL) *GHRH-arginine test*[1] *ITT* (peak cortisol < 18 µg/dL, peak GH < 3 µg/L)	
Kronvall 2016 [28]		3–6 months 6–12 months 12–14 months			GOS and age were related to PD at 3-6 months Lower general well-being scores were recorded in patients with PD at 3–6 months and 6–12 months

Table 1 (continued)

First author, year of publishing	Study design	Evaluation time following aSAH	Pituitary dysfunction and impaired axes	Hormonal evaluation methods	Predictors of pituitary dysfunction
Khajeh 2015 [10]	Prospective n = 84 (28 men) Mean age: 55.7 years	Baseline (n = 84) (32 days, mean)	Pituitary dysfunction 44% (32 days) GH insufficiency 31% ACTH insufficiency 1% FSH/LH insufficiency 34% TSH insufficiency 1%	*Baseline hormone concentrations* (TSH, fT4, testosterone (in males), LH, FSH, estradiol (in females), prolactin, cortisol, IGF-I, IGFBP3)	SAH-related complications (hydrocephalus, rebleeding, vasospasm, delayed cerebral ischaemia, intracerebral haematoma, hypertension, hyponatraemia) were related to higer risk of developing PD at baseline Hydrocephalus remained related to PD at 6th month GHD at 6th and 14th months was more frequent among male patients
		6 months (n = 72)	Pituitary dysfunction 26.2% (6 months) GH insufficiency 9.5% ACTH insufficiency 0% FSH/LH insufficiency 20% TSH insufficiency 1.2%	*Ghrelin test* (peak cortisol < 16 μg/dL) *GHRH-arginine test*[1]	
		14 months (n = 68)	Pituitary dysfunction 7% (14 months) GH insufficiency 6% ACTH insufficiency 0% FSH/LH insufficiency 5% TSH insufficiency 0%		
Goto 2016 [29]	Retrospective n = 59 (19 men) Mean age: 58 years	3–36 months	Pituitary dysfunction 15.1% GH insufficiency 15.1% ACTH insufficiency 0% FSH/LH insufficiency 0% TSH insufficiency 0% Hyperprolactinemia 5%	*Baseline hormone concentrations* (TSH, fT4, fT3, testosterone (in males), estradiol (in females), LH, FSH, prolactin, cortisol, ACTH, IGF-I, GH) *ITT* (peak GH < 1.8 ng/mL) *TRH, LHRH tests*	Surgical clipping was related to lower IGF-1 levels
Krewer 2016 [30]	Cross-sectional n = 106 (27 men) Mean age: 50 years	More than 1 year	Pituitary dysfunction NA GH insufficiency 10% ACTH insufficiency 29.1% FSH/LH insufficiency 21.6%(men), 12%(women) TSH insufficiency 15.5%	*Baseline hormone concentrations* (TSH, fT4, testosterone (in males), LH, FSH, estradiol (in females), prolactin, cortisol, IGF-I) *ACTH stimulation test* (peak cortisol < 18 μg/dL) *CRH stimulation test*(peak cortisol < 18 μg/dL) *GnRH stimulation test* (LH increase < 1.5-2 fold and LH increase < 20 U/L indicate deficiency in men and women, respectively) *GHRH-arginine test*[1] *ITT* (peak GH < 3 μg/L, peak cortisol < 18 μg/dL) *TRH test* (TSH increase < 2.0lU/mL indicate deficiency)	H&H and FS were not related to PD

Table 1 (continued)

First author, year of publishing	Study design	Evaluation time following aSAH	Pituitary dysfunction and impaired axes	Hormonal evaluation methods	Predictors of pituitary dysfunction
Vieira 2016 [31]	Prospective n = 92 (33 men) Mean age: 48.5 years	7.5 days (n = 82)	Pituitary dysfunction 48.8% (7.5 days) GH insufficiency 25.3% ACTH insufficiency 11.4% FSH/LH insufficiency 29.5% TSH insufficiency 6% Hyperprolactinemia 13.9%	*Baseline hormone concentrations* (TSH, fT4, T3, testosterone (in males), estradiol (in females), LH, FSH, prolactin, cortisol, ACTH, IGF-I, GH)	PD in acute phase was more prevalent in younger patients and patients with hydrocephalus PD in chronic phase was related to H&H score
		25.5 months (n = 68)	Pituitary dysfunction 25% (25.5 months) GH insufficiency 16.2% ACTH insufficiency 1.5% FSH/LH insufficiency 11.9% TSH insufficiency 0% Hyperprolactinemia 1.5%		
Giritharan 2017 [32]	Cross-sectional n = 100 (32 men) Mean age: 57 years	35 months (median)	Pituitary dysfunction 37% GH insufficiency 27% ACTH insufficiency 18% FSH/LH insufficiency 4% TSH insufficiency 0% Hyperprolactinemia 0%	*Baseline hormone concentrations* (TSH, fT4, testosterone (in males), estradiol (in females), LH, FSH, prolactin, cortisol, ACTH, IGF-I) *ACTH stimulation test*(250 µg) (peak cortisol < 16.3 µg/dL) *Arginine stimulation test* *Glucagon stimulation test* (peak cortisol < 16.3 µg/dL)	Hydrocephalus was associated with GHD

ACTH adrenocorticotropic hormone, *BMI* body mass index, *CBG* corticosteroid-binding globulin, *CRH* corticotropin releasing hormone, *DI* diabetes insipidus, *DHEAS* dehydroepiandrosterone sulphate, *FS* fischer score, *FSH* follicle-stimulating hormone, *fT3* free triiodothyronine, *fT4* free thyroxin, *GCS* glasgow coma score, *GH* growth hormone, *GHD* growth hormone deficiency, *GHRH* growth hormone-releasing hormone, *GnRh* gonadotropin-releasing hormone, *H&H* hunt and hess, *ICA* internal carotid artery, *IGF-1* insulin-like growth factor-1, *IGFBP-3* insulin-like growth factor binding protein-3, *ITT* insulin tolerance test, *LH* luteinizing hormone, *LHRH* luteinizing hormone releasing hormone, *NA* not available, *PD* pituitary dysfunction, *QoL-AGHDA* quality of life in adults with growth hormone deficiency, *SAH* subarachnoid hemorrhage, *SHBG* sex hormone binding globulin, *TRH* thyrotropin releasing hormone, *TSH* thyroid stimulating hormone, *TT4* total thyroxin, *17 β E2* 17 β-estradiol

[1]Cut-offs of GH according to BMI; BMI < 25 kg/m^2 : GH < 11 µg/L; BMI 25–30 kg/m^2 : GH < 8 µg/L and BMI > 30 kg/m^2 : GH < 4.2 µg/L

Pathophysiology of neuroendocrine changes and risk factors for aSAH

The mechanisms underlying the anterior pituitary dysfunction seen after aSAH are still unclear. Although various mechanisms such as direct mechanical trauma to the hypothalamus, pituitary stalk or the pituitary gland, vascular/ hypoxic insult to the hypothalamus or pituitary gland, inflammatory changes, compression from hemorrhage, edema or increased intracranial pressure, genetic predisposition and autoimmunity have been suggested for traumatic brain injuries (TBI) [38], much less is known for aSAH. The pathogenesis of aSAH induced hypopituitarism relates to the proximity of the circle of Willis to the hypothalamic-pituitary complex. Direct compression of the pituitary by the aneurysm itself (Fig. 1), ischemic injury in the very acute phase, increased intracranial pressure or surgical procedure related injuries or drugs have been suggested to alter pituitary functions after aSAH [14].

The high prevalence of abnormal laboratory values in the acute phase of aSAH may be physiological adaptation to critical illness [30]. However ongoing neuroendocrine changes seen later are probably due to ischemia induced damage. The unique portal system of the hypothalamohypophyseal unit makes it vulnerable to ischemia induced damage. The somatotroph cells are located in the lateral wings of pituitary and gonadotroph cells are scattered throughout pars distalis. They receive their blood supply from the long hypophyseal portal vessels. So these cells are more vulnerable to ischemia induced damage [39] explaining the higher frequency of GHD in these patients. Corticotrophs, located in the central wedge and pars intermedia, and the thyrotrophs, tending to cluster in the anteromedial portion of the gland, are thus in the less susceptible short hypophyseal portal territory.

Autopsy findings demonstrated ischemic necrosis, micro- and macrohemorrages in the hypothalamus of 68 of 102 patients with SAH [40]. Hypothalamic microhemorhages were found to be localized to paraventricular and supraoptic nuclei which was postulated to be a result of temporary obstruction of venous drainage in these nuclei due to increased pressure in the chiasmatic cistern after the hemorrhage. Direct damage of fine perforating hypothalamic arteries, ischemia due to vasoconstriction, subarachnoid blood forced up the sheaths of the perforating arteries and then rupturing out into the cerebral parenchyma were other suggested possible mechanisms [40]. Extravasated blood triggers a proinflammatory cascade which lead to various complications of aSAH besides its physical damage [41].

The discordance in the frequency of HPA axis dysfunction in TBI and SAH may be explained by a hypothalamic (rather than pituitary) dysfunction in SAH.

Studies have also looked for possible risk factors for hypopituitarism after aSAH. Age of the patient was shown to be significantly related to the prevalence of pituitary dysfunction in the acute phase [6]. The prevalence of pituitary dysfunction was found to be decreased by 2% for each increasing year of the patient [6]. These findings are in contrast to the results by Tanriverdi et al. that showed increasing age is associated with hypopituitarism in the acute phase [3]. In the follow up, a significant association between younger age and pituitary dysfunction was reported by Kronvall et al. [27].

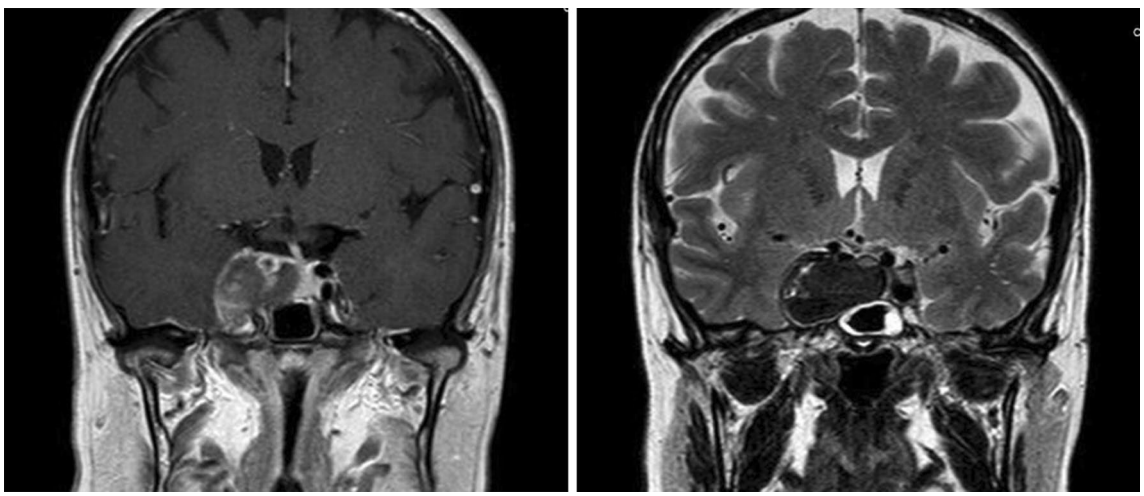

Fig. 1 Pituitary MRI images of a 60 year-old female patient. A large (3×2×2 cm) mass lesion had iso- and hyperintense areas on T1-weighted and iso- and hypointense areas on T2-weighted images. Aneurysmatic rupture obliterated right cavernous sinus and caused compression of the pituitary gland. She was admitted to the emergency department with the complaints of nausea, vomiting and diplopia. On physical exam she had cranial nerve 3, 4 and 6 palsies

Surgical clipping of the aneurysm has been shown to increase the risk of hypopituitarism. So surgical procedures may also be important in the development of hypopituitarism. However gender, systemic diseases such as diabetes and hypertension, smoking, Fisher and Hunt Hess score, location of the aneurysm were not found to influence the prevalence in the acute or chronic phase [6]. Goto et al. found GHD in five patients with aSAH who had a location of the aneurysm in the anterior cerebral and internal carotid artery [29]. However the number of patients is limited to make inferences.

Clinical severity of aSAH does not help to discriminate patients at high or low risk of developing hypopituitarism unlike TBI [12]. Inconsistent results are reported regarding predictive factors for hypopituitarism after aSAH. Female sex for ACTH deficiency [36], presence of cerebral vasospasm or hydrocephalus for hypopituitarism [10, 16] have been reported as possible risk factors. But the studies have different designs and not all parameters, that could be related to pituitary dysfunction after aSAH, are reported in the literature.

Impact of neuroendocrine changes on outcome of the patient

Hypocortisolemia in the acute phase of aSAH may lead to immediate complications and excess mortality. Weant et al. reported a subgroup of patients with relative adrenal insufficiency requiring hormonal replacement therapy with hydrocortisone to assist with inducing therapeutic hypertensive therapy [15]. Lack of dynamic endocrine testing in the acute phase of aSAH and exclusion of patients with poor neurological outcome after aSAH in prospective trials makes it difficult to ascertain the issue of HPA axis dysfunction [42]. Poll et al. has found that patients with normal diurnal serum free cortisol measurement had a significantly shorter intensive care unit-stay, less complications and more favorable outcome [18] (Table 2). However, the empirical glucocorticoid replacement which is not based on the presence of documented acute HPA axis dysfunction may be harmful or, at best, ineffective [43].

Some authors reported a significant association between pituitary dysfunction and patient outcome [17, 23]. Lammert et al. has shown that all patients with neuroendocrine dysfunction had impaired clinical outcome [20]. However, the prevalence of pituitary dysfunction was not found to be associated with the outcome of the patient in other studies [6, 12, 24].

Kreitchmann-Andermahr et al. demonstrated that endocrine disturbances contribute to the disturbed quality of life, depression and sleeping disturbances. Low basal cortisol level was associated with low quality of life scores and high depression scores. Severe GHD was associated with low scores of energy, quality of life, increased body mass index and waist hip ratio, and possibly associated with glasgow outcome scale (GOS) [32, 45]. A cross sectional study of 34 patients with TBI or aSAH demonstrated a relation between pituitary dysfunction and diminished functional performance 5–12 months after the event [11]. However this association was not adjusted for severity of TBI or aSAH. A prospective cohort in 51 aSAH patients reported an association between pituitary dysfunction and GOS score [26].

Further research is needed to understand the consequences of neuroendocrine changes on neurocognitive, emotional, and quality of life parameters. Correction of detected hormone deficiencies may favorably impact the outcome of patients with aSAH.

Diagnosis

Timing of assessment of pituitary function is an important factor affecting the prevalence of pituitary dysfunction [46]. An early assessment, particularly the first 3–6 months after the event, may lead to overestimation of pituitary dysfunction.

Diagnosis of adrenal insufficiency during the acute phase of aSAH is critical since it can be life threatening. Patients should be evaluated for signs and symptoms of hypocortisolism including hyponatremia, hypotension, and hypoglycemia. Morning serum cortisol level should be checked in the first days after aSAH [47]. Serum total cortisol values can be influenced by several factors including the degree of severity of the underlying illness, sepsis, and medications making it difficult to define a cortisol cut-off that will help diagnose adrenal failure in acute illness. Acute phase morning cortisol level of less than 7.2 µg/dL (200 nmol/L) may be suggestive of adrenal insufficiency in acutely ill patients with aSAH, and glucocorticoid replacement should be instituted. Morning cortisol level between 7.2 and 18 µg/dL (200–500 nmol/L) in the presence of features suggestive of adrenal insufficiency such as hyponatremia, hypoglycemia, hypotension, or unexpected slow recovery may still be inappropriately low and a trial of glucocorticoid therapy should be considered [12].

Due to lack of evidence for improved outcome by the treatment of GH, gonadotropin and TSH insufficiencies in the acute phase of aSAH, assessment of these axes is currently not recommended. Furthermore, the physiological response to acute and critical illness comprises hormonal changes similar to GHD, central hypogonadism and hypothyroidism.

Currently, no neurological or clinical parameters exist to accurately predict the presence of hypopituitarism after aSAH [34]. Between 3 and 6 months after injury, clinical

Table 2 Impact of pituitary dysfunction on outcome of aSAH

First author, year of publishing	Localization of SAH (%)	Treatment modality (Clipping/coiling)	Severity assessment		Outcome assessment tool	Evaluation of effect of PD on outcome (other endpoints)
Kreitschmann-Andermahr 2004 [13]	ACoA 35% MCA 17.5% ICA 12.5% PCoA 12.5% Other 22.5%	Not reported in exact numbers	H&H 1: 25% H&H 2: 30% H&H 3: 32.5% H&H 4: 12.5% H&H 5: 0%	FS 0: 7.5% FS 1: 10% FS 2: 15% FS 3: 60%	GOS	NA None of the clinical parameters predictive of a poor overall outcome after aSAH, most notably clinical grade on admission, amount of blood on initial CT scan, and patient age, showed any association with later neuroendocrine dysfunction
Dimopoulou 2004 [5]	ACoA 43.3% MCA 20% ICA 16.6% PCA 10% Other 10%	33.3% / 66.7%	H&H 1: 35.7% H&H 2: 42.8% H&H 3: 21.4% (n = 14, data of patients with PD)	FS 1: 21.4% FS 2: 64.2% FS 3: 7.1% FS 4: 7.1% (n = 14, data of patients with PD)	mRS Bartel index	PD was not related to functional outcome scores
Weant 2008 [15]	ACoA 27% MCA 19% PCoA 18% ICA 7%	50% / 44%	H&H 1: 6% H&H 2: 18.7% H&H 3: 50% H&H 4: 12.5%	FS 2: 6% FS 3: 75% FS 4: 19%	Hospital stay ICU stay Ventilator dependant days Vasopressor days	Baseline and stimulated cortisol levels were related to duration of hospital and ICU stay and mechanical ventilation
Jovanovic 2010 [16]	ICA 34.4% MCA 32.3% ACoA 23.7% VBA 9.7%	100%/0%	NA		GOS	Patients with isolated pituitary hormone abnormality had a lower GOS
Klose 2010 [17]	ACoA 39% MCA 31% ICA 11% Other 19%	53% / 47%	H&H 1: 30% H&H 2: 27% H&H 3: 20% H&H 4: 20% H&H 5: 3%	FS 0: 2% FS 1: 2% FS 2: 21% FS 3: 76%	GOS	Early PD was not related to GOS
Poll 2010 [18]	ACoA 45.5% MCA 22.7% Other 31.8%	NA	H&H 1: 18.2% H&H 2: 18.2% H&H 3: 18.2% H&H 4: 27.3% H&H 5: 18.2%	FS 1: 9% FS 2: 36.4% FS 3: 54.5%	GOS	Normal diurnal calculated free serum cortisol profile was associated with a shorter ICU-stay, less complications, better GOS on 7th day 8 a.m. cortisol was not associated with outcome
Lammert 2011 [19]	NA	75% / 25%	H&H 1: 37.5% H&H 2: 37.5% H&H 3: 16.7% H&H 4: 8.3%	FS 3: 83.3% FS 4: 16.7%	GOS	No association between PD and attention, memory, psychomotor deficits
Lammert 2012 [20]						PD was associated with lower GOS
Lanterna 2013 [23]	ACoA 50% Other 50%	18% / 8%	H&H 1: 50% H&H 2: 27% H&H 3: 23%	FS 1: 19.2% FS 2: 46.1% FS 3: 15.3% FS 4: 19.2%	GOS	Hypocortisolism was associated with poor outcome Cortisol peak at 5th day was correlated with risk delayed cerebral ischemia Cortisol concentration slope between 1 and 8 days was correlated with a poor outcome

Table 2 (continued)

First author, year of publishing	Localization of SAH (%)	Treatment modality (Clipping/coiling)	Severity assessment		Outcome assessment tool	Evaluation of effect of PD on outcome (other endpoints)
Pereira 2013 [24]	NA	81.8% / 18.2%	H&H 1: 48.4% H&H 2: 22.7% H&H 3: 19.6% H&H 4: 6% H&H 5: 3%	FS 1: 10.6% FS 2: 21.2% FS 3: 50% FS 4: 18.1%	GOS	PD was not associated with clinical outcome
Kronvall 2014 [26]	Circle of Willis 78% MCA 16% Pericallosal 6%	25% / 75%	H&H 1: 12% H&H 2: 41% H&H 3: 33% H&H 4: 14% H&H 5: 0%	FS 1: 0% FS 2: 16% FS 3: 55% FS 4: 29%	GOS	Patients with PD during acute phase had worse outcome at acute phase, but not at follow up Patients with PD at 3–6 months had worse outcome at follow-up
Kronvall 2015 [27]						PD was not related to outcome
Kronvall 2016 [28]						Patients with PD had lower general well-being scores at 3–6 months and 6–12 months
Khajeh 2015 [10]	Anterior circulation 58% Posterior circulation 42%	20% / 79%	GCS 13–15: 79% GCS 9–12: 13% GCS 3–8: 8%		QLS^{M}-H questionnare	Patients with PD had lower score on QLS at baseline but not at 6th or 14th months
Khajeh 2016 [44]					Fatigue Severity Scale	No effect of PD or GHD on long-term fatigue
Vieira 2016 [31]	ICA 38% ACoA 31.5% MCA 17.4% Other 13%	81.5% / 18.5%	H&H 1: 42.9% H&H 2: 30.8% H&H 3: 23.1% H&H 4: 2.2% H&H 5: 1.1%	FS 1: 12.1% FS 2: 25.3% FS 3: 41.8% FS 4: 20.9%	GOS mRS	PD was not associated with GOS, mRS
Giritharan 2017 [32]	ACoA 27% MCA 19% PCoA 18% ICA 7% Other 29%	15%/67%	WFNS 1: 69% WFNS 2: 13% WFNS 3: 4% WFNS 4: 3% WFNS 5: 6%	FS 1: 13% FS 2: 15% FS 3: 11% FS 4: 39%	GOS	GHD was not related to outcome

ACoA anterior communicating artery, *FS* Fischer score, *H&H* Hunt and Hess, *H&K* Hunt and Kosnik, *GCS* glasgow coma score, *GHD* growth hormone deficiency, *GOS* glasgow outcome scale, *ICA* internal carotid artery, *ICU* intensive care unit, *MCA* middle cerebral artery, *mRS* modified Rankin Scale, *NA* not available, *PCA* posterior cerebral artery, *PCoA* posterior communicating artery, *PD* pituitary dysfunction, *QLS^{M}-H* question on life satisfaction module-hypopituitarism, *VBA* vertebrobasilar artery, *WFNS* world federation of neurological surgeons

signs of hypopituitarism should be checked paying particular attention to loss of secondary hair, new oligomenorrhea/amenorrhea, impaired sexual function, weight changes, polydipsia, hyponatremia, hypotension, hypoglycemia or poor recovery. Pituitary assessment should be performed in the presence of these findings. However, the sequelae of brain injury may mask the signs of hypopituitarism, therefore in cases of uncertainty, hormonal assessment should be performed at least once [48].

After 3–6 months, an endocrine assessment with basal hormone levels should be carried out. For HPA axis, a basal cortisol level > 18 μg/dL is accepted as normal and < 3 μg/dL as abnormal. Between these levels dynamic assessment is required. Low dose (1 μg) ACTH test is a sensitive test and a peak cortisol level < 18 μg/dL is accepted as insufficient [46]. However, we have previously shown that the peak cortisol response can be as low as 12.5 μg/dL in healthy individuals [49]. If high dose (250 μg) ACTH test is used, a peak cortisol level < 18 μg/dL is accepted as insufficient. Glucagon stimulation test and ITT [23] have the advantage of evaluating both HPA and GH axes. Although ITT is accepted as the gold standard test, patients with aSAH may have epilepsy or at least may be prone to epilepsy which makes ITT contraindicated or relatively contraindicated for them. A peak cortisol response < 18 μg/dL is accepted as insufficient during ITT, however recent findings suggested lower cut-off levels for ITT to prevent overestimation of adrenal insufficiency [50, 51]. Glucagon is relatively a weak stimulant for HPA axis and a cortisol response < 10 μg/dL can be accepted as insufficient [52].

A combination of free T4 and TSH level is adequate for the evaluation of integrity of thyroid axis. A low free T4 in the presence of inappropriately normal or low TSH should be accepted as secondary hypothyroidism.

Symptoms and signs of hypogonadism are important in the assessment of gonadal axis. In a woman with past history of aSAH, if menstrual cycle is normal, no hormonal tests are needed. In post menopausal women and premenopausal women with menstrual irregularities low estradiol levels; and in men, repeatedly low testosterone levels in the presence of low or inappropriately normal gonadotropin levels (after exclusion of hyperprolactinemia) indicate secondary hypogonadism.

If all other pituitary axes are normal, a normal IGF-1 level according to age and sex reference is sufficient for the exclusion of GHD. If patient has panhypopituitarism and low IGF-1 level, GHD can be diagnosed. However, if IGF-1 level is low and other pituitary axes are normal, or IGF-1 is normal in the presence of other accompanying hormone deficiencies, then dynamic testing is required. Growth hormone testing should be performed after appropriate replacement of glucocorticoid and L-thyroxine. Insulin tolerance test, GST, GHRH-arginine or GHRH-GHRP-6 tests can be used. A peak GH level ≤ 3 μg/L during ITT or ≤ 1.1 μg/L during GST are accepted as GHD [3]. GHRH-arginine or GHRH-GHRP-6 tests body mass index specific cut-offs are suggested to be used [46]. However, GHRH and GHRP-6 are unavailable.

Reassessment of pituitary functions 1 year after aSAH would be appropriate in order to determine potential recovery and less commonly new-onset deficiencies [14, 20, 22, 27, 34, 42]. However, a laboratory value below a defined cut-off level may not necessarily reflect a clinically relevant hormone deficiency.

Treatment

The nonspecifity of the symptoms of hypopituitarism necessitate a through correlation with the degree of abnormalities in hormonal tests. Detection of adrenal insufficiency in the acute aSAH setting should be promptly treated as it may impact early outcome. In the subsequent months after aSAH, hormonal evaluation is recommended but treatment should be individualized. Treatments of hypocortisolemia and hypothyroidism are essential since these hormones are required for stress adaptation, cardiovascular and metabolic regulation.

On the other hand, gonadotropin deficiency seems to be transient in the acute phase and there is no clear evidence for the replacement of sex steroids in the acute phase of aSAH. Kopczak et al. gave testosterone replacement to 13 patients with low testosterone levels in a neurorehabilitaion unit about 1 month after the event. Four patients showed a Hb increase of > 2 g/dL, and 5 of them showed improvement of Barthel index > 20 points indicating possible benefits [30]. Randomized placebo controlled trials are necessary to further investigate the effect of hormonal suppletion after acute brain injury. If hypogonadism persists in the chronic phase, sex steroid replacement should be done as in other causes of hypogonadism. Treatment of GHD should be individualized according to symptoms, age and underlying disorders of the patient.

Posterior pituitary dysfunction

Posterior hypopituitarism leads to central diabetes insipidus (DI) and rarely potentially life threatening hypernatremia when associated with impaired thirst sensation or inadequate fluid intake. Aimeretti et al. reported 2.8% of DI in 32 SAH survivors after 12 months [14]. Diabetes insipidus was seen in 15% of cases after aSAH in the acute setting, which was associated with poorer patient outcome [53]. Adipsic DI has occasionally been reported after aSAH, in particular after clipping of anterior communicating artery aneurysms

[54–56], which is usually permenant and such patients are candidates for developing other hypothalamic abnormalities such as obesity and obstructive sleep apnea syndrome [57]. Diabetes insipidus in this situation was speculated to be a manifestation of acute elevation in intracranial pressure. The osmoreceptors receive their blood supply from small arteries arising from the anterior communicating artery and these vessels are assumed to be damaged during aneurysm clipping, with infarction of the circumventricular organs where the osmoreceptors are sited [58]. Patients with DI are treated with desmopressin by a dose proportional to the degree of DI. A dose per week can be skipped in order to prevent the development of iatrogenic hyponatremia. Patients with adipsic DI are required to be managed by a combination of regular desmopressin and fixed fluid intake, with regular measurements of plasma sodium concentration [59].

Hyponatremia is very common after aSAH seen in 30% of patients [53, 60]. Mild hyponatremia (Na < 135 mmol/L) was detected in 57%, moderate-severe hyponatremia (Na < 130 mmol/L) in 20% of 316 aSAH patients in a retrospective study [61] and the high rate of hyponatremia (50% of patients < 135 mmol/L) was confirmed in a later prospective study [62]. The most common cause for hyponatremia was syndrome of inappropriate antidiuretic hormone secretion (62–72% of cases) and hyponatremia was associated with longer hospital stay but not with mortality [61, 62]. Hyponatremia was not found to be associated with any particular site of aneurysm or method of aneurysm management [61, 62]. See et al. demonstrated an association of old age with hyponatremia and smoking habit with longer duration of hyponatremia [63]. Diabetes insipidus is usually transient after aSAH in majority of cases [14], but sometimes persist up to 3 months [9].

Nevertheless, hypernatremia may be more predictive for mortality than hyponatremia in patients with aSAH [59, 64, 65]. On the other hand, correct management of hyponatremia is important since it is responsible for one of six readmissions after hospital discharge of patients with aSAH [66]. A metaanalysis of steroid therapy following aSAH demonstrated lower rates of hyponatremia with fludrocortisone or hydrocortisone supplementation [67]. The cause of hyponatremia and the velocity of development are important for the management. If hyponatremia develops over several days, brain adaptation occurs which prevents development of cerebral edema. In case of acute hyponatremia cerebral edema may develop so it should be corrected promptly and effectively. Initial correction of 3–5 mmol/L over 2–4 h is essential to reduce cerebral edema [68]. For severe symptoms, 100 mL of 3% saline over 10 min can be given and repeated 3 times until clinical improvement and then the targeted Na level can be reached in the next 24 h. For milder symptoms, 3% saline infusion rate can be 0.5–2 mL/kg/h. Plasma Na rise should be < 8 mmol/24 h and should not exceed 12 mmol/24 h in order to prevent osmotic demyelination [59].

Conclusion

Hypopituitarism seems to be a common complication of aSAH. The course of hypopituitarism may be dynamic with recovery and deterioration of hormone deficiencies in the follow up. In the immediate period after aneurysm rupture, ACTH deficiency and disorders of water balance have the priority of detection after aSAH. The reported prevalence rates vary considerably due to different dynamic tests and cut-offs used in the studies. Screening for hypopituitarism after aSAH should be carried out despite lack of gold standard evaluation tests and cut-off values in the follow up, because missed diagnosis may lead to untoward consequences. However, a laboratory value below a defined cut-off level may not necessarily reflect a clinically relevant hormone deficiency.

Compliance with ethical standards

Conflict of interest Zuleyha Karaca, Aysa Hacioglu, Fahrettin Kelestimur declares that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the only patient whose MR imaging was included in the review.

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