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Research Paper

Evaluation of Neuroendocrine Dysfunction Following Acute Aneurysmal Subarachnoid Hemorrhage

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ABSTRACT

Background and Aim: In the management of aneurysmal subarachnoid hemorrhage (aSAH), endocrine dysfunction is infrequently considered. Pituitary (neuroendocrine) dysfunction is highly prevalent after aSAH, leading to residual symptoms such as decreased cognition and quality of life. Although hypopituitarism following SAH may present with non-specific subtle symptoms, it can lead to potentially serious consequences if left undiagnosed.

Methods and Materials/Patients: This study was performed to observe the incidence and pattern of neuroendocrine alterations in cases of acute aSAH. A total of 25 patients with acute SAH within 7 days of ictus were included in this prospective study, and an endocrine assessment was performed. The pituitary axes were evaluated for possible dysfunctions, including somatotropic, gonadotropic, corticotropic, and thyrotropic axes.

Results: A total of 25 SAH cases (10 males and 15 females; mean age 55.24 years) were included in the study. Aneurysms were more commonly found in the anterior circulation (n=22) than in the posterior circulation (n=3). Most of the patients presented with the Hunt-Hess grade of 1, followed by grades 3, 2, and 4, respectively. Growth hormone deficiency (48%) was the most common pituitary dysfunction, followed by adrenocorticotrophic hormone (24%), gonadotropins (FSH/LH) (24%), and thyroid stimulating hormone (16%) deficiencies, respectively. Single pituitary axis neuroendocrine dysfunction was noted in 9 patients (36%) and multiple pituitary axes dysfunction was observed in 8 patients (32%). Overall, 17 patients (68%) had neuroendocrine dysfunction in single or multiple pituitary hormone axes.

Conclusion: Neuroendocrine dysfunction in acute aSAH is 68%. Accordingly, 32% of the participants had single-axis pituitary dysfunction and 36% had multiple axes pituitary dysfunction. The most common endocrine dysfunction was growth hormone deficiency (48%), followed by adrenocorticotrophic hormone, gonadotropins (LH & FSH), and thyroid stimulating hormone. Therefore, it is suggested to include hormonal evaluation in the management of acute SAH for better clinical outcomes.

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Highlights

• There is an increased incidence of neuroendocrine dysfunction following aneurysmal SAH (aSAH), mostly during the acute phase.

• Multiple pituitary hormone deficiencies and single-axis pituitary dysfunction were noted in 36% and 32% of patients, respectively.

• The most common pituitary hormone deficiency following aSAH was growth hormone (48%), followed by adrenocorticotrophic hormone, gonadotropins (LH/FSH), and thyroid stimulating hormone.

• In the clinical management of aSAH, clinical outcome benefits from the evaluation of hormonal status.

Plain Language Summary

This study aims to investigate the pattern of hormone dysfunction in the case of subarachnoid hemorrhage (SAH) following the rupture of aneurysms. The pituitary hormones, including growth hormone, gonadotropins (FSH/LH), adrenocorticotrophic hormone, and thyroid stimulating hormone were studied for possible dysfunction. A total of 25 patients, comprising 10 males and 15 females with a mean age of 55.24 years, were included in this study. Most cases presented with the Hunt-Hess grade I, followed by grade III (20%). The most common neuroendocrine deficiency was the growth hormone in 48% of the patients, followed by the adrenocorticotrophic hormone (24%), the gonadotropins (FSH/LH) (24%), and thyroid stimulating hormone (16%) deficiency, respectively. Single pituitary hormone deficiency was observed in 17 cases (68%). Endocrine dysfunction is an important complication of SAH. This study concludes that pituitary hormone dysfunction is highly prevalent in aneurysmal SAH. This leads to residual symptoms, such as decreased cognition and quality of life. Although hypopituitarism following SAH presents with subtle nonspecific symptoms, it can lead to serious consequences if left undiagnosed. Therefore, it is suggested to include hormonal evaluation in the management of aneurysmal SAH for better clinical outcomes.

1. Introduction

Subarachnoid hemorrhage (SAH) is a life-threatening condition that occurs because of the accumulation of blood between the arachnoid and the pia mater. Although most SAH is traumatic in etiology, aneurysmal SAH (aSAH) occurs in a small proportion of this patient population. This is the most worrisome type of SAH. Aneurysmal rupture is suspected in spontaneous SAH. As a worldwide health burden, aSAH poses a high fatality risk and permanent disability rates. The incidence of aSAH is 6-10/100000 per year, with the commonly affected age group of 40 to 60 years. [1] Ruptured cerebral aneurysms account for about 75% to 85% of SAH for non-traumatic SAH. There is about a 50% mortality rate after 6 months. As it affects the patients during their most reproductive years, aSAH has major implications on social, functional, and economic aspects [2]. The first 6 months after the event of aSAH is termed the acute phase and the period after 6 months is termed the chronic phase [2].

Endocrine dysfunction is an uncommon and unusual consideration in the management of aSAH [3, 4, 5]. There are limited studies, including small series and patient case reports, which show the association of aSAH with neuroendocrine dysfunction [6-17]. Such limited systematic studies that investigate this topic have yielded conflicting results. However, many of the previous studies have been performed after at least 1 year following SAH, and the number of studies done in cases of acute SAH is considerably scarce [17]. This study aims to investigate the incidence, pattern, and magnitude of neuroendocrine changes occurring in cases of acute aSAH.

2. Methods and Materials/Patients

We aimed to evaluate the pattern and incidence of neuroendocrine dysfunction in cases of acute aSAH. This prospective observational hospital-based study was conducted in the Department of Neurosurgery, Government Medical College, India. All adult patients (age >18 years) admitted with aSAH in the Department of Neurosurgery, Government Medical College, Calicut, India from August 2019 to July 2020 were included in

this study. Patients with ictus of SAH for more than 7 days, on drugs affecting hypothalamic-pituitary function, or with a pre-existing pituitary disorder were excluded from this study. The patients were included after giving an informed consent letter. The data on age, sex, clinical severity of SAH at the time of admission (by the Hunt-Hess grading system), location of the aneurysm, and the modality of treatment (embolization or surgery) were noted. A computed tomography (CT) scan and digital subtraction angiography (DSA) of the cerebral circulation were used for radiological evaluation. On the day after admission, the serum hormone level assessment was done during morning hours (8:00 to 9:00) and the following hormones were measured: thyroid stimulating hormone (TSH), free thyroxine, cortisol, growth hormone (GH), prolactin, insulin-like growth factor 1 (IGF-1), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone (males)/ estrogen(females). The endocrine evaluation was done on the next day after admission in the morning between 8:00 and 9:00 and it included the measurement of the following hormones: TSH, free thyroxine, cortisol, GH, prolactin, IGF-1, FSH, LH, and testosterone (males)/estrogen (females) [17]. The statistical analysis was done using the SPSS software version 20 and the Chi-square test was also utilized in the analysis.

The posterior pituitary deficiency was not evaluated. The endocrine assessment was performed through laboratory tests using commercially available diagnostic kits, which included the following items:

Serum thyroxine (normal range: 4.8–12.7 µg/dL) ;

Serum TSH (normal range: 0.5-5 µU/mL);

Cortisol (0800 h: 171-536 nmol/L);

IGF-1 (age- and gender-specific normative data were used) ;

Prolactin (men: 4.0-15.2 ng/mL and women: 4.79-23.3 ng/mL) ;

LH (men: 1.7-8.6 mIU/mL and women: 2.4-12.6 mIU/mL);

FSH (men: 1.5-12.4mIU/mL and women: 3.5-12.5 mIU/mL, postmenopausal >30 mIU/L)

Testosterone (9.9-27.8 nmol/L) ;

Estradiol (12.5-166 pg/mL) [18].

Meanwhile, the definitions of endocrine abnormalities were done using certain criteria:

Secondary hypothyroidism was defined as T_4 level <4.8 µg/dL with low/normal TSH level [18];

Central hypogonadism was defined as serum testosterone <9 nmol/L in the presence of low or normal levels of LH (men) [19]; 17 β estradiol levels <12 pg/mL in the presence of low or normal gonadotropins (women) [18]; and, low or inappropriately normal gonadotropins for age (FSH <30 mIU/L) in postmenopausal women [19];

Serum prolactin levels <5 ng/mL in either sex were considered low.

Relevance of the study

The relevance of this study is to assess hormonal dysfunction in patients following acute aSAH. This study helps to analyze the incidence and pattern of neuroendocrine dysfunction following aSAH and evaluate various factors associated with the disease. Meanwhile, this study helps to predict the course of disease and prognosis concerning the hormonal dysfunction following SAH. Even though a few previous studies exist on this topic, the available studies were mostly from western literature. From our literature review, we could not find any similar study from Kerala published in the medical literature. Overall, the study recognizes the need for hormonal evaluation in SAH, which may benefit the clinical outcomes and help the patients have a better quality of life following aSAH.

3. Results

A total of 25 cases admitted with aSAH in the Department of Neurosurgery, Government Medical College, Calicut, India from August 2019 to July 2020 were included in this study. Cases were selected according to the predetermined inclusion and exclusion criteria. These cases were subjected to thorough clinical and endocrine assessments. The participants included 10 males and 15 females with a male/female ratio of 2:3. The overall Mean±SD age was 55.24+12.39 years (Table 1 A).

The most common location of aneurysms was found to be in the anterior circulation (n=22) rather than the posterior circulation (n=3) [17]. The distribution of aneurysms based on the involved blood vessels in the decreasing order of frequency is as follows: anterior

Table 1. Patients' demographics

Table 1A. Mean±SD age and gender distribution of aSAH cases

Gender	No. (%)	Mean±SD
Male	10(40)	53.20±9.99
Female	15(60)	56.60±15.71
Total	25	55.24±12.39

Table 1B. Grades of SAH

SAH	No. (%)
1.00	13(52.0)
2.00	2(8.0)
3.00	9(36.0)
4.00	1(4.0)

Table 1C. Number of days of SAH from admission to investigation

	Mean±SD
Days	2.64±0.86

communicating artery (A.COM)–8 [18]; middle cerebral artery (MCA) –8 [18]; internal carotid artery (ICA)–4; superior cerebellar artery (SCA)–2; basilar artery (BA)–2; and vertebral artery (VA)–1 (Figure 1, Table 1B).

The grading of SAH was done using the Hunt-Hess classification. The distribution SAH grades is as follows: grade 1=52%, grade 3=36%, grade 2=8%, and grade 4=4% (Table 1C).

The endocrine evaluation showed the deficiency of certain hormones during the acute phase of aSAH. Among 25 patients, 17 cases had one or more pituitary hormone deficiencies; that is, the incidence of pituitary dysfunction during the acute phase of aSAH in our study

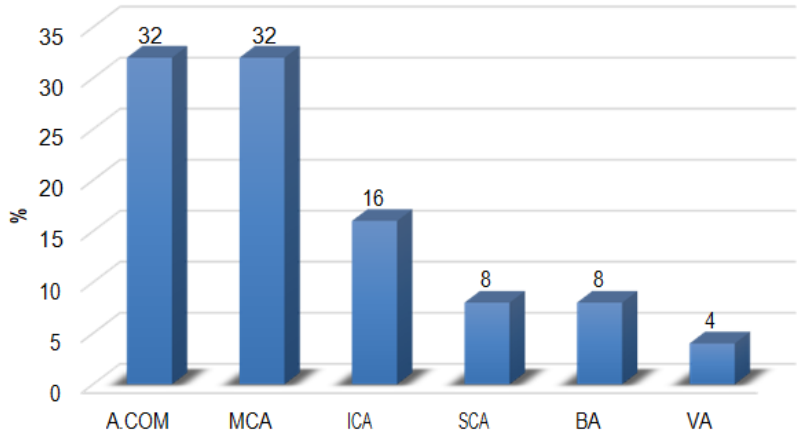

Figure 1. Distribution of aneurysms based on the involved vessels

A.COM: Anterior communicating artery; MCA: Middle cerebral artery; ICA: Internal carotid artery; SCA: Superior cerebellar artery; BA: Basilar artery; VA: Vertebral artery.

Table 2. Hormonal disturbance of ACTH, GH, Cortisol, TSH, LH, FSH, and Prolactin

Hormones	Hormone Status	NO. (%)
ACTH	Normal	19(76.0)
	Decreased	6(24.0)
GH	Normal	13(52.0)
	Decreased	12(48.0)
Cortisol	Normal	25(100)
	Decreased	0(0)
TSH	Normal	21(84.0)
	Decreased	4(16.0)
LH	Normal	19(76.0)
	Decreased	6(24.0)
FSH	Normal	19(76.0)
	Decreased	6(24.0)
Prolactin	Normal	25(100)
	Decreased	0(0)

ACTH: Adrenocorticotropic hormone; GH: Growth hormone; TSH: Thyroid stimulating hormone; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone.

was 68%. Among this population, 9 cases (36%) had single pituitary axis deficiency and 8 cases (32%) had deficiencies in multiple pituitary axes. In addition, 6 cases (24%) showed ACTH deficiency (Table 2). GH deficiency was noted in 12 cases (48%) and cortisol was normal in all the cases and no cortisol deficiency was observed

Table 3. Association between grades of SAH and hormones

SAH	No. (%)													
	ACTH		GH		Cortisol		LH		FSH		Prolatin		TSH	
	N	D	N	D	N	D	N	D	N	D	N	D	N	D
1.00	11(57.9)	2(33.3)	8(61.5)	5(41.7)	13(52)	0	10(52.6)	3(50)	10(52.6)	3(50)	13(52)	0	10(47.6)	3(75)
2.00	2(10.5)	0	0	2(16.7)	2(8)	0	2(10.5)	0	2(10.5)	0	2(8)	0	2(9.5)	0
3.00	5(26.3)	4(66.7)	4(30.8)	5(41.7)	9(36)	0	6(31.6)	3(50)	6(31.6)	3(50)	9(36)	0	8(38.1)	1(25)
4.00	1(5.3)	0	1(7.7)	0	1(4)	0	1(5.3)	0	1(5.3)	0	1(4)	0	1(4.8)	0
P	0.31		0.28		-		0.71		0.71		0		0.74	

ACTH: Adrenocorticotropic hormone; GH: Growth hormone; TSH: Thyroid stimulating hormone; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone.

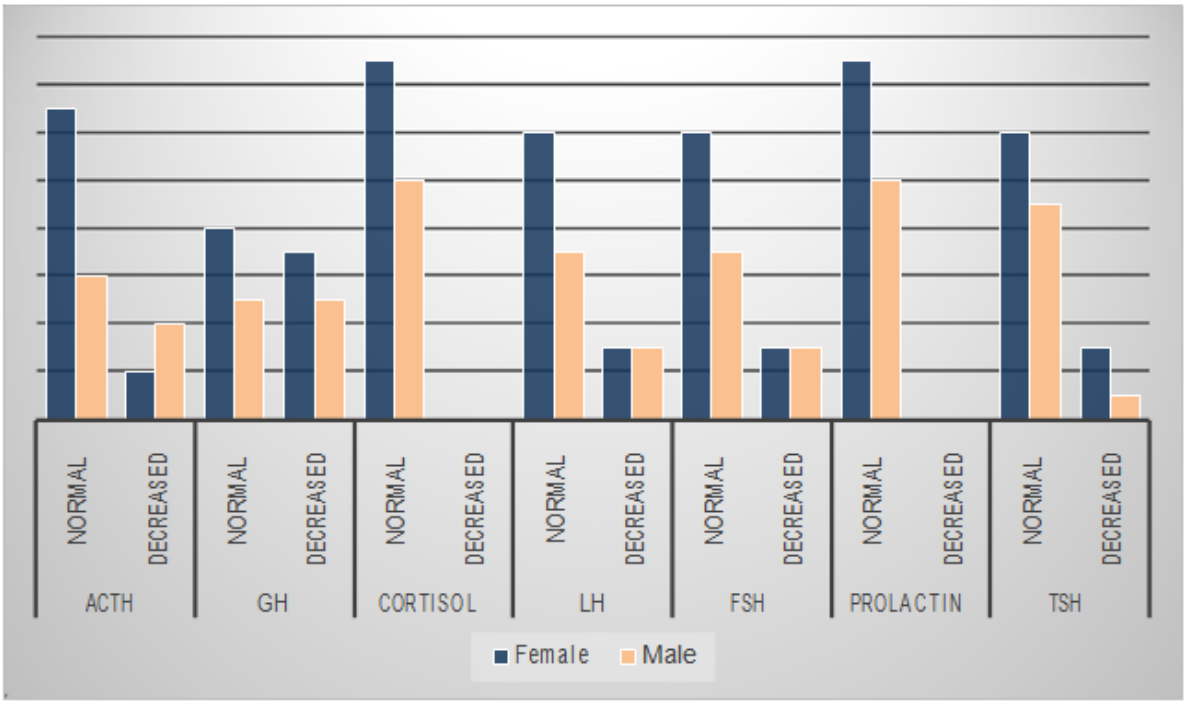

Figure 2. Association between gender and hormones among aSAH cases

ACTH: Adrenocorticotropic hormone; GH: Growth hormone; TSH: Thyroid stimulating hormone; LH: Luteinizing hormone; FSH: Follicle stimulating hormone; aSAH: Aneurysmal subarachnoid hemorrhage.

(Table 2). LH deficiency was reported in 6 cases (24%) and FSH deficiency in 6 cases (24%). Prolactin levels were normal in all of the patients. Four patients (16%) had TSH deficiency (Table 2). Accordingly, GH deficiency (48%) was the most common pituitary dysfunction in our study, followed by ACTH (24%), FSH/LH (24%), and TSH (16%).

Table 1 C displays the days from the SAH admission to the investigation. The Mean±SD period of investigation was 2.64±0.86 days after admission.

According to the above data, it can be inferred that the most common hormonal deficiency during the acute phase of aSAH was GH (48%), followed by ACTH (24%), LH (24%), FSH (24%), and TSH (16%). Table 3 shows the association between the grades of SAH and hormones. There is no correlation between the grades of SAH and hormonal deficiencies. Although the hormonal deficiencies of ACTH, GH, LH, FSH, and TSH can be observed in grade 1 and grade 3 SAH, this association is insignificant as the P>0.05.

Figure 2 presents the association between gender and hormones among aSAH cases. Among the cases with ACTH deficiency, 33.3% were female and 66.7% were male (P=0.14). Of all patients with GH deficiency, 58.3% were female and 41.7% were male (P=0.59). Among the patients with gonadotropin (LH/FSH) deficiency, half were female and half were male (P=0.45). Moreover, 75% of the patients with TSH deficiency were female and the rest (25%) were male (P=0.46). This association between gender and hormonal deficiency in aSAH is considered insignificant as the P>0.05.

Table 3 indicates the association between the blood vessels involved in aSAH and hormonal disturbances. ACTH deficiency was noted in 6 aSAH cases involving anterior circulation, and none involving posterior circulation. ACTH deficiency was noted in 2 A.COM, 2 MCA, 1 ICA, and 1 SCA involvement (P=0.88). GH deficiency was noted in 10 aSAH cases involving anterior circulation and 2 aSAH cases involving posterior circulation; meanwhile, GH deficiency was noted in 3 A.COM, 4 MCA, 3 ICA, 1 BA, and 1 VA involvement (P=0.48). Gonadotropin (LH/FSH) deficiency was observed in 6 aSAH cases involving anterior circulation, and none involving posterior circulation. Additionally, gonadotropin (LH/FSH) deficiency was seen in 2 A.COM, 2 MCA, 1 ICA, and 1 SCA involvement (P=0.88). TSH deficiency was reported in 4 aSAH cases involving anterior circulation (3 A.COM and 1 MCA), and none involving posterior circulation (P=0.47) (Figure 3). However, this association between

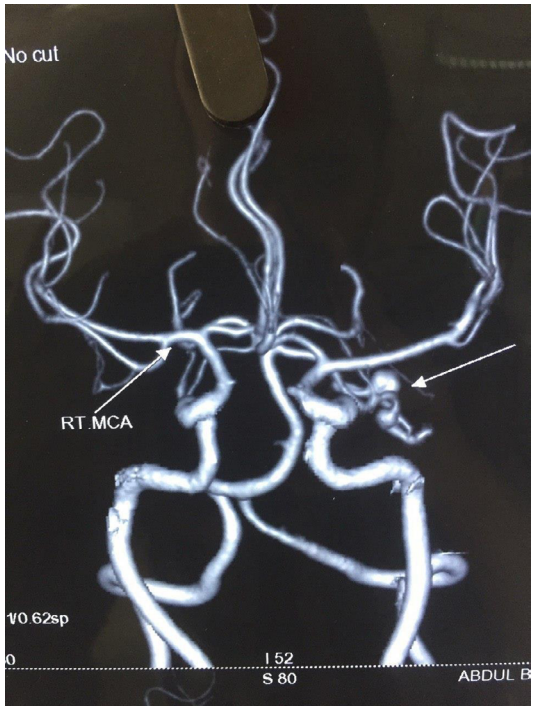

Figure 3A. Computed tomography angiogram with 3D reconstruction showing the location of aneurysm

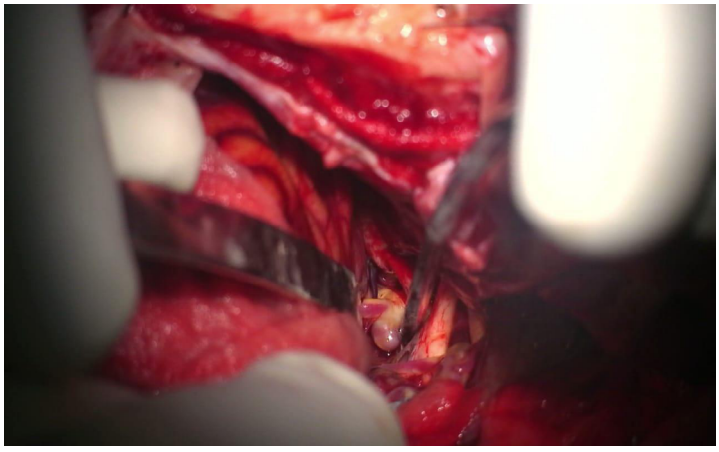

Figure 3B. Intraoperative photograph of cerebral Aneurysm

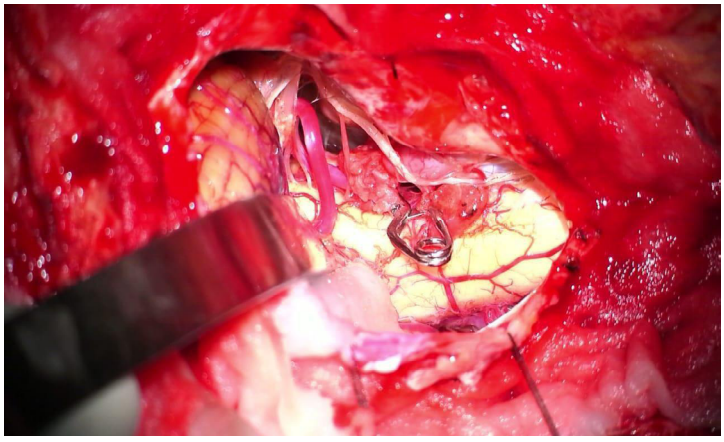

Figure 3C. Intraoperative photograph of clipped aneurysm

the involved blood vessels and hormonal disturbances was not significant as the P>0.05.

4. Discussion

There is a limited number of studies, including small series and case reports of patients which suggest the association between aSAH and neuroendocrine dysfunction [6-17]. Such a limitation in investigating this topic has produced contradictory results [17]. A similar study was conducted by Osterman in 1975 on 50 patients, after 3.5 months following SAH [15] The circadian rhythm of plasma 11-hydroxycorticosteroids and the Metyrapone test were used to assess the hypothalamic-pituitary-adrenal (HPA) axis [17]. Gonadal and thyroid functions were assessed clinically and by the corresponding baseline hormones [17]. The study reported that endocrine abnormalities were uncommon; that is, 6% of the cases had abnormal circadian rhythm in cortisol, 11% displayed a pathological Metyrapone test, 2% showed mild thyroid function abnormalities, whereas no hypogonadism was observed [14, 17]. Kreitschmann-Andermahr et al. studied 21 patients between 14 and 43 months following aSAH [9]. A combination of thyrotropin-releasing hormone–LH-releasing hormone Arginine test and the insulin Tolerance test were used to assess the pituitary function. In this study, isolated or combined endocrine abnormalities were found in 43% of the patients, which included ACTH (n=4) or GH deficiency (n=3), and ACTH plus GH impairment (n=2) [7, 22]. Brandt et al. evaluated 10 cases, 12 months following aSAH by performing routine laboratory investigations and Dynamic tests [4]. A significant number of patients (50%) had some deficiency of pituitary hormone [4]. Abnormalities included isolated or combined somatotroph and gonadotroph deficiencies, whereas thyroid and adrenal functions were preserved in all the cases [4, 17].

Dimopoulou_et al. evaluated 30 patients between 12 and 24 months following aSAH and reported that endocrine abnormalities commonly affect 47% of the screened SAH patients. This series manifested the most common endocrine alteration of GH deficiency, as reflected by low levels of IGF-1 in a substantial proportion of patients. Although it is often recommended to perform a dynamic assessment of GH reserve to assess the somatotroph function, currently there is considerable evidence that low IGF-1 levels represent a good marker of GH deficiency. Hypogonadism followed GH deficiency in this study. The Dynamic testing to assess the cortisol level was done using a low-dose (1 µg) ACTH Stimulation test. This test is agreed as a reference standard for evaluating the HPA axis, as it closely correlates with the insulin-induced Hypoglycemia test. The study reported diminished cortisol response in only 3 patients; however, this observation is especially important because if cortisol deficiency is unrecognized, it may lead to serious untoward consequences, especially if the patient is unable to cope with a stressful situation [9, 17].

Experimental SAH studies conducted in porcine animal models have expressed that endocrine stress responses begin within 15 minutes of the hypothalamic-pituitary-adrenal (HPA) axis with early peaks of ACTH, cortisol, and aldosterone. In addition, early activation of the sympathetic nervous system has been observed [19].

A prospective observational study by Khajeh et al. (2014) analyzed the incidence and course of anterior pituitary dysfunction following aSAH [20]. Fasting state endocrine functions were measured at the baseline, 6 months, and 14 months intervals [20]. The study included 84 patients and their Mean±SD age was 55.8+11.9 years [20]. It was reported that 39% of the cases had pituitary dysfunction in one or more axes at baseline, 26% after 6 months, and 7% after 14 months [20]. The most common deficiencies were gonadotropin (34%) and GH deficiency (31%) [20]. The baseline evaluation was performed in the meantime of 32 days. Gonadotropin deficiency was detected in 34% of patients. All the female participants with gonadotropin deficiency were postmenopausal, with a Mean±SD age of 58+10 years. GH deficiency was identified in 31%, TSH deficiency in 1%, and ACTH deficiency in 1%. The prevalence of hypopituitarism after SAH was more than its prevalence in the normal population. It has been observed that pituitary dysfunction decreases over time and the occurrence of pituitary dysfunction is associated with complications and severity of symptoms related to SAH [18]. This implies a causal relationship between hypopituitarism and SAH. [18] This study concludes that pituitary dysfunction is a significant complication in SAH survivors. In addition, hydrocephalus is an independent clinical predictor of long-term pituitary dysfunction following SAH [20].

GH and/or gonadotropin deficiency occurs more frequently than TSH or ACTH deficiencies, according to many studies. This observation suggests that the anterior lobe of the pituitary gland is more vulnerable to damage secondary to SAH, as it predominantly consists of thyrotropin, somatotropic, and gonadotropic cells [20]. This could probably be because of the differences in the position of pituitary parts within the skull, or variations in the vascular supply [20]. The anterior pituitary lobe receives blood from the long pituitary por-

tal vessels which traverse from above the diaphragma sellae, while the remaining parts of the pituitary gland receive blood from the middle and inferior pituitary arteries [20]. Acute hormonal deficiencies can be caused as a result of pressure effects, vasospasm, bleeding, or ischemia, which can be reversible with the treatment; therefore, certain hormonal deficiencies get recovered gradually [18]. However, during later stages, an infarct or any structural damage can occur in the HPA axis and new hormone deficiency eventually occurs or becomes permanent [18]. These could be the possible reasons for recovery or occurrence of the new-onset hormone deficiency [18].

While pituitary dysfunction recovers in a majority of patients during follow-up, it persists in a small proportion of patients [20]. Some findings suggest the possibility of regeneration of the adult pituitary gland following injury, which might explain the recovery of pituitary function [18]. Early screening for pituitary dysfunction might be beneficial in the long-term following SAH [20]. Symptoms pertaining to GH deficiency, such as low energy levels, fatigue, and cognitive function decline of memory and planning are often found after SAH, which might hamper the process of rehabilitation [20].

A study by Pinaki Dutta et al. (2012) compared the hormonal deficiencies between the patients with the middle cerebral artery and anterior communicating artery aSAH and concluded that there was no difference in endocrine abnormalities between the two groups [18]. It suggested that hormonal deficiency cannot be aptly correlated with the aneurysmal location [18]. Furthermore, no correlation was observed between the severity of the hormonal deficiency and the clinical severity of the SAH grade (as determined by the Hunt-Hess scale), as well as the radiological grade of SAH [18]. This study included 60 aSAH patients (37 males and 23 females) and their Mean±SD age was 44.9±13.1 years [18]. Also, 12 out of 23 females were postmenopausal. Among the 60 patients, 23 cases were because of MCA aneurysm rupture and 37 cases were because of A.COM aneurysm rupture [18]. The GH status as determined by the Mean±SD IGF-1 levels was normal (149.00±16.30 ng/dL) at ictus, but it decreased to 96.10±56.35 ng/mL after 6 months (P=0.05) [18]. At ictus, 8 cases were found to have hypogonadism, and at the 6-month follow-up, only 4 patients showed hypogonadism, all of which were new-onset hypogonadism [18]. GH deficiency was depicted by lower values of gender and age-adjusted values of IGF-1 [18]; namely, 7 patients had GH deficiency at ictus, and 5 patients had GH deficiency after 6 months among which 2 cases were new-onset GH deficiency while the remaining 3 cases had continued GH deficiency since ictus [18]. Central hypothyroidism, as depicted by low T_4 levels, was found in 3 patients initially [18]; among them, 2 cases recovered but one case had persistent hypothyroidism after 6 months. Overall, at the 6-month follow-up after aSAH, 31.6% of cases had one or more hormonal deficiencies. Central hypogonadism was the most common hormone deficiency (36.6%), followed by GH deficiency (15%) [18]. One observation was that although pituitary dysfunctions are statistically insignificant between the two compared groups, prolactin deficiency and the syndrome of inappropriate antidiuretic hormone secretion were found to be more commonly associated with patients having A.COM aSAH. The study further recommends that all the patients must be subjected to endocrine assessment, not only at the baseline but also after 6 to 12 months [18].

A study by Pereira et al. (2013) included 66 aSAH patients who underwent pituitary hormonal evaluation within the first 15 days. The Mean±SD duration during which the endocrine assessment was done was 7.4±6.6 days after aSAH, compared to 2.64+0.86 days in the present study. The study by Pereira and colleagues included 66.7% females, 33.3% males, and the Mean±SD age of the patients was 48.3±13.8 years, which is comparable with our study with 60% females, 40% males, and the Mean±SD age of 55.24+12.39 years. The incidence of pituitary dysfunction in the study by Pereira et al. was 59.1%, while it was 68% in our study. According to the above study, the most common hormonal deficiency was that of gonadotropins (LH/FSH, 34.8%), followed by GH (28.7%), ACTH (18.1%), and TSH (9%). Whereas in our study, GH deficiency (48%) was the most common pituitary dysfunction, followed by ACTH (24%), FSH/LH (24%), and TSH (16%). Pereira et al. study showed multiple pituitary axis deficiencies in 25.7% of the patients, while in our study it was noted in 32% of the cases. Also, their study showed a greater incidence of hormone dysfunction in patients with the Glasgow Coma Scale (GCS) <13, Hunt-Hess grade>4, and Fisher grade 4 [21]. There was no significant association between hormone deficiency and increased hospitalization or clinical outcome [21]. Our study further reported no significant correlation between hormonal deficiencies with gender, grade of SAH, or blood vessel involvement of the aneurysm [21].

Another comparable study was done by Klose et al.(2010) that assessed the hormonal changes in 26 aSAH patients at the Mean±SD of 7 days after the onset [22]. The incidence of pituitary dysfunction was 58% and the study showed

FSH/LH deficiency in 93.3% of patients, low T_3 in 35%, low cortisol in 12%, and low GH/IGF-1 in 15% [21, 22].

Posterior pituitary deficiency is primarily depicted by sodium imbalance secondary to antidiuretic hormone (ADH) dysfunction [21]. We did not evaluate posterior pituitary deficiency in our study because its dysfunction is already known and expected in SAH patients and individuals subjected to neurosurgical interventions [21].

Our study is also comparable to the study by Jaiswal et al., which was a prospective study including 100 aSAH cases that underwent detailed clinical and endocrine evaluation during the acute phase. There were 38% males and 62% females. This female preponderance has been observed in many studies, including ours. The mean age of the patients was 43.6 years [17]. The location of aneurysms in the anterior circulation (n=95) included the following items: MCA-15, A.COM-49, P.COM-16, ICA-9, anterior choroidal artery-1, distal anterior cerebral artery-5 [23]. The location of aneurysms in the posterior circulation (n=5) included basilar artery - 4, and posterior cerebral artery-1 [23]. Aneurysms were more common in the anterior circulation (n=22) than posterior circulation (n=3). This was similar to our study with the following order of distribution: A.COM–8, MCA–8, ICA–4, SCA–2, BA–2, and VA–1 [18]. Jaiswal et al. study has reported GH as the most common hormone deficiency, followed by gonadotropin, corticotrophin, and thyrotropin; whereas the order of frequency of hormone deficiency in our study was GH, corticotrophin, gonadotropin, and thyrotropin. Their study, however, showed hyperprolactinemia in 10 cases, which was not observed in our study. In addition, their study showed single pituitary axis dysfunction in 26% and multiple pituitary axes dysfunctions in 67% of cases [23], while in our study single pituitary axis dysfunction was observed in 9 cases (36%) and multiple pituitary axes dysfunction in 8 cases (32%) [23]. In the research performed by Jaiswal et al., 93% of cases of acute SAH had endocrine dysfunction, while our study reported an incidence of 68%. It is thereby suggested that hormonal evaluation must be considered a part of management in acute aSAH conditions [17].

Kronvall et al. reported the prevalence of pituitary dysfunction as 37% during acute aSAH. Furthermore, the data suggested a worse clinical outcome associated with pituitary dysfunction, being more common among patients with bleeding sites closer to the hypothalamus [23].

5. Conclusion

Neuroendocrine dysfunction occurs in 68% of aSAH cases during the acute phase. Accordingly, 32% among them have single-axis pituitary dysfunction and 36% have multiple axes pituitary dysfunction. The most common endocrine dysfunction in this study is GH deficiency (48%), followed by ACTH, gonadotropins (LH & FSH), and TSH. Therefore, it is suggested that including the hormonal evaluation in the management of acute aSAH may benefit the clinical outcomes.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Institutional Ethics Committee of the Government Medical College, Kozhikode, Kerala, India (Code: GMCKKD/RP 2020/IEC/221 dated 08/08/2019). Written informed consent form was obtained from all patients who participated in this study.

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Authors' contributions

Conception and design: Harikrishnan Sreenivasan and Rajeev Mandaka Parambil; Data collection: Prakasan Kannoth, Shanavas Cholakkal, Ebby Kachirayil Sebastian; Data analysis and interpretation: Harikrishnan Sreenivasan, Shanavas Cholakkal; Drafting the article: Prakasan Kannoth and Ebby Kachirayil Sebastian; Critically revising the article: Harikrishnan Sreenivasan and Shanavas Cholakkal; Reviewing the submitted version of the manuscript: Harikrishnan Sreenivasan and Rajeev Mandaka Parambil; Final version approval: Rajeev Mandaka Parambil.

Conflict of interest

There is no conflict of interest concerning this study.

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