

Prognostic Assessment of Endocrine Disturbances in Posttraumatic Subarachnoid Hemorrhage

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Abstract

Traumatic subarachnoid hemorrhage (SAH) is a condition with high risk for the development of hypopituitarism. Hormonal assessment is not a part of routine assessment after traumatic SAH. This study is a prospective screening study from our center focusing on the prognostic assessment of endocrine disturbances in posttraumatic SAH. A total of 150 consecutive patients with head injuries with SAH were included irrespective of their age and sex. Patients were divided into three groups: with normal hormonal status (group 1), patients with endocrine disturbances with no hormonal replacement (group 2), and patients with endocrine disturbances with replacement therapy (group 3). Hormonal assessment was done within 24 hours of admission and repeated at 7 to 15 days and at 1-month interval. Most commonly affected was pituitary-thyroid axis, and the most common hormone to increase was cortisol. In group 3, a statistically significant improvement was seen in Glasgow outcome score (GOS) as compared with the other two groups at 1 month. A statistically significant positive correlation has been found between thyroxine (T_4) at 30 days and Glasgow coma scale (GCS) at discharge in group 3, a negative correlation has been found between GCS at admission and serum cortisol at days 7 to 15 in group 3. A positive correlation has been found between GCS at admission and GOS at 1 month in group 3. The authors have demonstrated evidence of pituitary dysfunction following traumatic brain injury (TBI) with SAH. Patients with traumatic SAH should be screened for hypopituitarism, so that appropriate hormone replacement is given to improve the outcome of these patients.

Keywords

- head injury
- subarachnoid hemorrhage
- endocrine dysfunction
- hormone replacement

Introduction

Traumatic brain injury (TBI) is one of the causes of disability and mortality in developing country population, causing physical impairment to long-term cognitive, behavioral, psychological, and social alteration.¹ Cyran in 1918 first reported hypopituitarism following TBI.² Hypopituitarism following traumatic subarachnoid hemorrhage (SAH) can be partial or complete with prevalence ranging from 38 to 55%. However, this range varies according to studies.^{3–7} In patients with traumatic SAH, the neuroendocrine axis may be affected by direct compression of the hypothalamus or pituitary gland as a result of mechanical insult or as a result of secondary insult from hypoxia, anemia, elevated intracranial pressure, and brain edema.³ Many of the long-term symptoms

after SAH have similar features occurring in patients with untreated hypopituitarism. Adrenocorticotrophic (ACTH) and thyroid-stimulating hormone (TSH) deficiency may cause fatigue, weakness, headache, altered mental activity, and impaired memory. Growth hormone (GH) deficiency may cause lack of vigor, fatigue, decreased exercise tolerance, and decreased social functioning. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiencies in women lead to oligomenorrhea, dyspareunia, infertility, and loss of libido.⁸ Testosterone deficiency in men can present with impaired sexual functioning, mood impairment, and loss of libido. Therefore, neuroendocrine dysfunction may be the cause or a contributing factor for residual symptoms after SAH, and neuroendocrine evaluation has to

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be performed in SAH patients. Despite evidence, studies are not available, and hormonal assessment is not a part of routine diagnostic after traumatic SAH. This study is a prospective screening study from our center focusing on the prognostic assessment of endocrine disturbances in posttraumatic SAH.

Material and Methods

The study was conducted in Department of Neurosurgery, SMS Medical College and Hospital, Jaipur, during November 2015 to November 2016.

Inclusion Criteria

A total of 150 consecutive patients with head injuries with SAH were included irrespective of their age and sex.

Exclusion Criteria

Patients with the following conditions were excluded from the study:

- Metabolic disorder.
- Altered coagulation profile.
- Cardiac disease and comorbid illness.
- Spontaneous SAH.
- Preexisting hormonal dysfunction.

Computed tomography (CT) scan at the time of admission and standard treatment guidelines were followed as per requirement. Data were recorded in proforma. All patients with traumatic SAH underwent basal hormonal evaluation within the first 24 hours of the admission to the neurosciences intensive care unit (NICU) or neurosurgery department. Basal hormone levels including free triiodothyronine (ft_3), free thyroxine (ft_4), TSH, prolactin (PRL), cortisol, LH, GH, FSH, and testosterone were measured and repeated at 7 to 15 days and at 1 month. All hormonal assessment was done in morning hours. Blood was drawn by venipuncture and centrifuged at 3,000 rpm (revolutions per minute) for 10 minutes, and serum was stored at 22°C until further processing. The hormones were measured by electrochemiluminescence with Immulite2000 analyzer (Siemens). Normal ranges of hormonal levels for ft_3 (1.8–4.2 ng/mL), ft_4 (0.89–1.76 ng/dL), TSH (0.4–4.0 uIU/mL), FSH (0.7–11.1 mIU/mL), LH (0.8–7.6 mIU/mL), cortisol (5–25 µg/dL), GH (1–10 ng/mL), PRL (1.9–25 ng/mL), and testosterone (72–853 ng/dL) were taken normal as per patients' age and sex. Patients were categorized into three groups: with normal hormonal status (group 1), patients with endocrine disturbances with no hormonal replacement (group 2), and patients with endocrine disturbances with replacement therapy (group 3). Patients were randomized in groups 2 and 3 by using odd and even number randomization. Outcomes of these groups were measured using Glasgow outcome score (GOS). The data collected are subjected to statistical analysis. Parametric tests are used for analysis of continuous variable whereas chi-square and other nonparametric tests are used for qualitative data. Pearson correlation test is also used to calculate correlation coefficient. $p < 0.05$ is taken as significant.

Results

A total of 150 patients were included in the study. There were 113 males and 37 females, with the age range between 10 and 5 years. The most common mode of injury was road traffic accident followed by fall from height. Of the 150 patients, 52 had no endocrine disturbances (group 1), 48 had endocrine disturbances and were not given any hormonal replacement (group 2), and 50 patients had endocrine disturbances with replacement therapy for thyroid and cortisol accordingly (group 3). In group 1, 10.42% had severe, 33.3% had moderate, and 64.58% had mild TBI. In group 2, 16.67% had severe, 33.33% had moderate, and 50% had mild TBI. In group 3, 30% had severe, 54% had moderate, and 16% had mild TBI. In group 1, 94.23% had good GOS and 5.77% had poor GOS. In group 2, 83.33% had good GOS and 16.67% had poor GOS. In group 3, 50% had good GOS and 50% had poor GOS. There is no statistically significant difference in baseline characteristic of the three groups (►Table 1). However, these data show that there were more patients in moderate and severe category with endocrine dysfunction.

Hormone Profiles

In group 2 of the 48 patients on day 1, percentage of the patients showing low-hormone profile of ft_3 was in 54.17% patients, ft_4 in 39.58%, TSH in 45.83%, cortisol in 4.17%, and PRL in 2.08%, gonadotrophins (LH, FSH) in 25% and 6.25%, and testosterone in 14.63%, whereas 12.50% patients have increase in cortisol level (►Table 2). In group 2, of the 45 patients on days 7 to 15, percentage of the patients showing low-hormone profile of ft_3 was in 40% patients, ft_4 in 24.44%, TSH in 28.89%, cortisol in 2.22%, gonadotrophins (LH, FSH) in 22.22% and 4.44%, and testosterone in 25%, whereas 13.33% patients have increase in cortisol level (►Table 2). In group 2, of the 43 patients after 1 month, percentage of the patients showing low-hormone profile of ft_3 was in 32.56%, ft_4 in 13.95%, TSH in 6.98% and gonadotrophins (LH, FSH) in (13.95% and 2.32%), and testosterone in 7.89%, whereas 13.95% patients have increase in cortisol level (►Table 2). The most common hormonal axis affected was pituitary-thyroid, with maximum decrease in ft_3 within 24 hours, and the most common hormone to increase was cortisol, with maximum increase within 24 hours. Five patients expired. In group 3, of the 50 patients on day 1, percentage of the patients showing low-hormone profile of ft_3 was in 40% patients, ft_4 in 64%, TSH in 30%, cortisol in 6%, PRL in 2% and gonadotrophins (LH, FSH) in (8% and 2%), and testosterone in 10.53%; 20% patients have increase in cortisol level (►Table 3). In group 3, of the 36 patients on days 7 to 15, percentage of the patients showing low-hormone profile of ft_3 was in 11.11% patients, ft_4 in 27.78%, TSH in 5.56%, and testosterone in 13.33%; 8.33% patients have increase in cortisol level (►Table 3). In group 3, of the 36 patients after 1 month, percentage of the patients showing low-hormone profile of ft_4 was in 8.33% patients, FSH in 2.78%, and testosterone in 3.45%. No patient has increase in cortisol level (►Table 3). The most common hormonal axis affected was pituitary-thyroid, with maximum decrease in ft_4 within 24 hours, and the most common

Table 1 Baseline characteristics of the study population

	Group 1		Group 2		Group 3		Total	p Value
Age groups (y)	No.	%	No.	%	No.	%		
10–20	14	29.17	11	22	6	12	31	0.06 NS
21–30	17	35.42	8	16	14	27	39	
31–40	7	14.58	9	18	9	17	25	
41–50	7	14.58	6	12	7	13	20	
51–60	6	12.50	11	22	4	8	21	
61–70	1	2.08	2	4	7	13	10	
> 70	0	0.00	1	2	3	6	4	
Age (y)	34.60 ± 14.75 (13–70)		36.67 ± 17.05 (6–70)		38.02 ± 18.68 (10–85)			0.58NS
Sex								
Female	10	20.83	15	0.3	12	0.23	37	0.37 NS
Male	42	87.50	33	0.66	38	0.73	113	
Mean GCS at admission	12.23 ± 3.43		11.32 ± 2.98		12.65 ± 3.003		12.07 ± 3.2	0.095 NS
Mortality	3	5.76	5	10.41	14	28		

Abbreviations: GCS, Glasgow coma scale; NS, not significant.

hormone to increase was cortisol, with maximum increase within 24 hours. Fourteen patients expired. The patients were given thyroxin in a dose of 50 µg once daily whereas prednisolone in a dose of 5 mg once daily with a tapering dose over 1 week in thyroid and cortisol deficiency, and were monitored later.

Correlation of Individual Groups with Glasgow Outcome Score at 1 month and Glasgow Coma Scale at the Admission

In groups 1 and 2, no significant correlation found between GCS at admission and GOS after 1 month. In group 3, a statistically significant positive correlation has been found between GCS at admission and GOS at 1 month (correlation coefficient 0.828 with $p < 0.05$). A statistically significant positive correlation has been found between T_4 at 30 days and GCS at discharge in group 3 (correlation coefficient 0.198 with $p = 0.025$). A negative correlation has been found between GCS at admission and serum cortisol at days 7 to 15 in group 3 (correlation coefficient -0.466 with $p = 0.004$).

Effect of Hormone Replacement on Glasgow Outcome Score

In group 3, a statistically significant improvement was seen in GOS as compared with the other two groups at 1 month with a p value of 0.035 (►Fig. 1). No patient was found to have GOS-2 in any group.

Discussion

Posttraumatic endocrine disturbances are a clinically significant complication following traumatic head injury with SAH.²⁻⁷ Most studies on pituitary dysfunction after TBI have focused on head injury not on traumatic SAH, and most of them are retrospective.^{3,4,6,9} This study is a prospective study from a

tertiary care center evaluating the pituitary functions and the need of replacement and assessing the prognostic effect of endocrine disturbances in posttraumatic SAH. Pituitary response to traumatic event and several changes become apparent during this phase.^{3,4} There is a recent increase in recognition of neuroendocrine disturbances due to awareness of the condition, prolonged survival, and improved intensive care management.¹⁰⁻¹² Several mechanisms have been suggested for this hypothalamic-pituitary dysfunction due to TBI, including hypoxic insult or direct mechanical injury to the hypothalamus, pituitary stalk or pituitary gland, compression from hemorrhage, edema or raised intracranial pressure, and vascular injury to the hypothalamus or the pituitary gland.^{3,13,14} Rotational acceleration-deceleration can cause shearing injury to the axons, and it is commonly seen in midline structures of the brain and may be the possible mechanism of hypothalamic pituitary dysfunction after TBI.¹⁵ The prevalence of endocrine disturbances following TBI in this study (after 1 month) is in accordance with previous studies, in which the prevalence has ranged from 11 to 69.6%.^{4,9} Wartofsky and Burman have reviewed the effects of severe illness on thyroid function and have described nonthyroidal illness, also known as *euthyroid sick syndrome*.¹⁶ This includes patients with low T_3 and normal T_4 . In this study, the authors have found 14.25% and 12.24% patients in groups 2 and 3, respectively, with this finding; however, Lieberman et al have found 11.6% patients in their study whereas Kelly et al have found only 4.5% in this group. The authors have found a statistically significant positive correlation between T_4 at 30 days and GCS at discharge in group 3. The authors have given thyroid supplement in the dose of 50 µg thyroxin once daily in group 3 patients. Pituitary-thyroid axis is the most commonly affected axis in this study, which is in accordance with the study by Benvenega et al. Some studies have shown that somatotrophic-gonadotrophic axes are the most commonly

Table 2 Hormone distribution in group 2

	Group 2					
	24 h (n = 48)		7–15 d (n = 45)		30 d (n = 43)	
T ₃	No.	(%)	No.	(%)	No.	(%)
High	0	0.00	0	0.00	1	2.33
Low	26	54.17	18	40.00	14	32.56
Normal	22	45.83	27	60.00	28	65.12
T ₄						
High	0	0.00	4	8.89	1	2.33
Low	19	39.58	11	24.44	6	13.95
Normal	29	60.42	30	66.67	36	83.72
TSH						
High	1	2.08	0	0.00	0	0.00
Low	22	45.83	13	28.89	3	6.98
Normal	25	52.08	32	71.11	40	93.02
Cortisol						
High	6	12.50	6	13.33	6	13.95
Low	2	4.17	1	2.22	0	0.00
Normal	40	83.33	38	84.44	37	86.05
FSH						
High	3	6.66	2	4.44	1	2.32
Low	3	6.25	2	4.44	1	2.32
Normal	42	93.33	41	91.11	41	95.34
LH						
High	3	6.25	2	4.65	1	2.32
Low	12	25.00	10	22.22	6	13.95
Normal	33	68.75	33	73.33	36	83.72
Prolactin						
High	1	2.08	1	2.22	3	6.98
Low	1	2.08	0	0.00	0	0.00
Normal	46	95.83	44	97.78	40	93.02
GH						
High	3	6.25	2	4.44	2	4.65
Normal	45	93.75	43	82.22	41	81.40
Testosterone-only males	n = 41		n = 32		n = 38	
Low	6	14.63	4	12.50	3	7.89
Normal	35	85.37	28	87.50	35	92.11

Abbreviations: FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; PRL, prolactin; GCS, Glasgow coma scale; T₃, triiodothyronine; T₄, thyroxine; TSH, thyroid-stimulating hormone.

affected axes at 1 year following the injury.^{3,4} The authors have not found any patients in groups 2 and 3 with low GH. In acute phase of trauma, low or high basal GH levels associated with low insulin-like growth factor 1 (IGF-1) levels have been demonstrated.¹⁷ The authors have not measured IGF-1 levels in this study. Feibel et al have reported elevated serum cortisol levels during initial phase of trauma, which gradually declines over a period of time.¹⁸ The authors have found 12.50% and 20% patients in groups 2 and 3 with elevated

cortisol level within 24 hours of admission. This high level of cortisol may be responsible for catabolic response to trauma. According to King et al, this response may persist up to 4 months.¹⁹ The authors also found 4.17% and 6% patients in groups 2 and 3 with low cortisol within 24 hours. In group 3, prednisolone replacement was given in the dose of 5 mg once daily, then gradually tapered over 1 week. The authors have found a negative correlation between GCS at admission and serum cortisol at days 7 to 15 in group 3. Hyperprolactinemia

Table 3 Hormone distribution in group 3

	Group 3					
	24 h (n = 50)		7–15 d (n = 36)		30 d (n = 36)	
T ₃	No.	(%)	No.	(%)	No.	(%)
High	0	0.00	0	0.00	0	0.00
Low	20	40.00	4	11.11	0	0.00
Normal	30	60.00	32	88.89	36	100.00
T ₄						
High	0	0.00	0	0.00	0	0.00
Low	32	64.00	10	27.78	3	8.33
Normal	18	36.00	26	72.22	33	91.67
TSH						
High	1	2.00	2	5.56	0	0.00
Low	15	30.00	2	5.56	0	0.00
Normal	34	68.00	33	91.67	36	100.00
Cortisol						
High	10	20.00	3	8.33	0	0.00
Low	3	6.00	0	0.00	0	0.00
Normal	37	74.00	33	91.67	36	100.00
FSH						
High	4	8.00	4	11.11	4	11.11
Low	1	2.00	0	0.00	1	2.78
Normal	45	90.00	32	88.89	31	86.11
LH						
High	4	8.00	2	5.55	1	2.77
Low	4	8.00	0	0.00	0	0.00
Normal	42	93.33	34	94.44	35	97.22
PRL						
High	1	2.00	0	0.00	0	0.00
Low	1	2.00	0	0.00	0	0.00
Normal	48	96.00	36	100.00	36	100.00
GH						
High	6	12.00	5	13.89	5	13.89
Normal	44	88.00	31	86.11	31	86.11
Testosterone-only males	n = 39		n = 30		n = 29	
Low	4	10.53	4	13	1	3.45
Normal	35	92.11	26	87	28	96.55

Abbreviations: FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; PRL, prolactin; GCS, Glasgow coma scale; T₃, triiodothyronine; T₄, thyroxine; TSH, thyroid-stimulating hormone.

occurred in 2.08% and 2% in groups 2 and 3; however, Lieberman et al have found 10% patients with hyperprolactinemia in their study. Hypothalamic and pituitary stalk lesions have been reported at autopsy of patients who died after TBI, and lesion in either may be responsible for elevation in PRL level.²⁰ PRL is the only hormone tonically inhibited by hypothalamus; thus, increase in level may be associated with its injury.²¹ Edward and Clark have also mentioned this in their study. The normal serum PRL in most of these cases may be

due to nonhypothalamic injury. Early gonadotrophin suppression is well known in critical illness, and it has been suggested to be a part of a physiologic response to the stress caused by acute illness and may even play a role in inflammatory response.²² Testosterone is an anabolic steroid, and suppression of its secretion in acute stress could also be an appropriate response to diminish the energy consumption.²³ Such gonadotrophin disturbances have also been shown in patients soon after TBI.¹⁷ It may take some time for

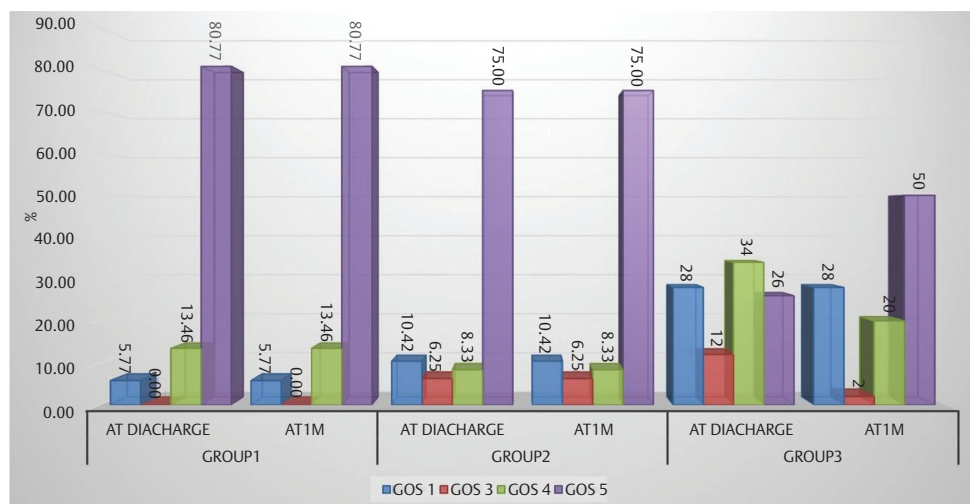


Fig. 1 Comparative analysis of Glasgow outcome score at discharge and 1 month. GOS, Glasgow outcome score.

the pituitary to recover and gonadotrophin function to normalize.²⁴ Another reason for the recovery of pituitary function with time has been suggested to be the regeneration of the severed portal vessels as they grow down into the damaged part of the anterior lobe. In this study, the authors find 25%, 6.25% and 2%, and 8% patients with low gonadotrophs (LH and FSH) in groups 2 and 3, but they have not replaced this hormone and have only monitored their outcome and have found a decreasing trend in gonadotrophins levels in groups 2 and 3. They have only measured testosterone levels in males and also found a similar decreasing trend that is in accordance with previous studies.^{17,22} Patients with hypopituitarism require replacement of the deficient hormone as a part of their standard clinical care. Hormone replacement can reverse the symptoms of hypopituitarism and normalize the risks associated with it.⁸ In patients with brain injury, damage to the pituitary may be subtle, and sometimes only borderline endocrine disturbances are present. In addition, these patients often have multiple other sequelae of the trauma. It is not clear whether these patients benefit from hormone replacement in the same way as patients with classic causes of hypopituitarism.⁸ Because of the potential serious consequences of cortisol and thyroid deficiency, it is important to adequately treat these patients if convincing biochemical and clinical evidence of these deficiencies are present. Gonadotrophic hormone deficiency is often transient in the early period after brain injury, and it needs to be monitored. The authors have found a positive correlation between GCS at admission and GOS at 1 month in patients undergoing hormone replacement. In group 3 patients, the authors have found a significant improvement in GOS following replacement as compared with group 2.

Strengths of the Study

The strength of this study is the design. It is a single-center prospective study. Standardized evaluation was performed on all patients for assessment of the hormonal axis, the most complicated axis to assess.

Limitations of the Study

This study only assessed the benefit of hormone replacement on GOS at a maximum of 1 month. However, longer follow-up and assessment of cognition, rehabilitation, body composition, and neuropsychiatric functions are also required.

Conclusion

The authors have demonstrated evidence of pituitary dysfunction following TBI with SAH. They believe that screening for neuroendocrine function is justified in these patients. However, it remains unclear when such evaluation should be done as recovery commonly occurs within 3 to 12 months. The authors suggest that evaluation of the pituitary function should be performed frequently after the injury. However, clinical assessment might be indicated earlier to evaluate the need for neuroendocrine evaluation. Furthermore, it is of great importance to identify potential predictive factors for screening of these patients. Randomized studies are needed to assess the effects of replacement of these hormones in the case of subtle endocrine abnormalities, transient endocrine changes, and when clinical features of deficiency are unclear.

Conflict of Interest

There is no conflict of interest among the authors.

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