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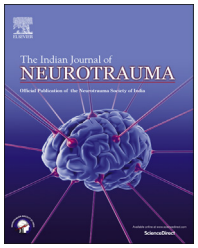

Original Article

Endocrine dysfunction following traumatic brain injury in acute stage

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ABSTRACT

Aim: Only few studies of hormonal dysfunction in acute setting after traumatic brain injury (TBI) are available in literature with variable results. The aim of the present study was to determine the incidence of anterior pituitary hormone deficiencies, and correlate with in hospital mortality.

Methods: This study was carried out on 30 patients with moderate to severe TBI presenting within 24 h of injury. Chemiluminiscence immunoassay using an automated chemiluminiscence analyser was used to determine the basal hormone levels. Thyroid stimulating hormone (TSH), prolactin (PRL), cortisol, growth hormone (GH), and testosterone in males or luteinizing hormone (LH) and follicle stimulating hormone (FSH) in females were measured.

Results: Out of the 30 cases, 12 cases underwent surgery for various reasons. Six patients expired, and all of them had a poor GCS at presentation (mean 4.8 ± 0.9). In the acute setting high cortisol level showed a trend towards significance ($p = 0.097$) in terms of mortality. Other hormonal levels were also found to be abnormal, but no conclusion could be drawn due to small number.

Conclusion: Anterior pituitary hormone imbalance is common after TBI in acute setting. Elevated cortisol is associated with increased mortality.

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1. Introduction

Traumatic brain injury (TBI) has become increasingly common. About 180–250 persons per 100,000/year die or are hospitalized in industrialized countries as a result of TBI, and survivors are left with significant adverse physical and/or psychological sequelae.[1] Because the majority of TBI survivors are young adults with near-normal life expectancy, the implications of undiagnosed posttraumatic pituitary dysfunction may contribute to morbidity associated with TBI. Though posttraumatic pituitary dysfunction was recognized more than 80 years ago, but it was thought to be a rare occurrence, despite autopsy results showing pituitary gland necrosis in up to one third of patients who suffered fatal head injury.[2] Recent data suggest that pituitary dysfunction is not infrequent among TBI survivors, with as many as 40–50% of patients studied reported having some degree of pituitary dysfunction.[3] Only few studies of hormonal dysfunction in acute setting after moderate and severe TBI are available in literature.[4,5] The aim of the present study was to determine the incidence of anterior pituitary hormone deficiencies in the acute phase after TBI, and correlate basal hormone levels with mortality.

2. Methods

2.1. Clinical

This is a prospective study of 30 patients with TBI who were evaluated and treated within 24 h of injury at our institute during June 2010 to Dec 2010. The study was undertaken following clearance from the Institutional Scientific Ethics Committee. Initial clinical data was collected as per the neurotrauma proforma of our institute. Patients with severe (Glasgow coma scale (GCS) 3–8) and moderate (GCS 9–12) TBI were included in study. All patients underwent a CT scan of head and were treated accordingly. Outcome was assessed in terms of in hospital mortality. Patients with following were excluded: polytrauma with significant other system involvement; glucocorticoid treatment within 3 weeks or growth hormone (GH) treatment within 12 months; a history of cranial irradiation; pre-existing pituitary, thyroid, or adrenal diseases; severe cardiac, renal or hepatic diseases; sepsis; substance abuse, cancer, and any neurological or psychiatric illness.

2.2. Hormonal analyses

All patients underwent a basal hormonal evaluation immediately following admission, within 24 h of injury. The samples were collected between 7.00 and 9.00 A.M. Following hormones were measured: thyroid stimulating hormone (TSH), prolactin (PRL), cortisol, growth hormone (GH), and testosterone in males or luteinizing hormone (LH) and follicle stimulating hormone (FSH) in females. Dynamic tests were not performed. Free T3 was not measured. The tests were carried out at Central Lab, Bangalore. Chemiluminiscence immunoassay using an automated chemiluminiscence analyser was used to determine the hormone levels. The reference ranges used are shown in Table 1.

Table 1 – Laboratory reference range for serum hormone levels.

Hormone	Reference range
Serum cortisol	5–23 μg/dl
Growth hormone-basal (serum)	
• Male	0.1–3.8 ng/dl
• Female	0.1–7.0 ng/dl
TSH	
• Child	0.9–8.1 uIU/ml
• Adult	0.5–4.5 uIU/ml
Prolactin	
• Child	3.2–20 ng/ml
• Adult	2.0–18.0 ng/ml
Testosterone	
• Child	0.02–0.25 ng/ml
• Adult	2.8–8.0 ng/ml
FSH	
○ Day III	3–20 mIU/ml
○ Follicular phase	3.5–12.5 mIU/ml
○ Luteal phase	1.7–7.7 mIU/ml
○ Mid cycle	4.7–21.5 mIU/ml
○ Post menopausal	25.8–134.8 mIU/ml
LH	
○ Day III	<7 mIU/ml
○ Follicular phase	2.4–12.6 mIU/ml
○ Luteal phase	1.0–11.4 mIU/ml
○ Mid cycle	7.7–58.5 mIU/ml

2.3. Statistical analysis

SPSS 17.0 was used for data analysis. (SPSS 17.0 program, SPSS, Inc., Chicago, IL, USA; Feature 1200- SPSS Statistics Base 17.0: Local license for version 17.0- Network Expiration : none). Univariate analysis was carried out using the Mann–Whitney U test, Wilcoxon W test and Pearson Chi-square test. Proportions were compared by Chi Square test and the mean by Mann–Whitney, $p < 0.05$ was taken as a significant value.

3. Results

The demographic profile of patients is shown in Table 2. The patient's ages varied from 6 years to 80 years. Majority of the

Table 2 – Demographic profile of patients. SD – standard deviation.

Age (years) (mean ± SD)	38.9 ± 19.1
Sex	23 (76.7%) Male
Time of presentation (hours) (mean ± SD)	5 ± 4
Mode of injury	Road traffic accident 80% Fall 10% Others 10%
Glasgow coma scale (GCS) at presentation (mean ± SD)	7.6 ± 2.4
Severe (GCS 3–8)	18 (54%)
Moderate (GCS 9–12)	12 (36%)

Table 3 – Neuroendocrine changes in acute traumatic brain injury.

Study	Number	Time to Testing	GCS score	Test used	Neuroendocrine axis assessed				
					Adrenal	GH	Thyroid	Gonadal	Prolactin
Feibel,[4] 1983	23	12–36 h	<8	Basal ACTH + Cortisol	↑Cortisol despite ↑dose dexamethasone	N/A	N/A	N/A	N/A
Hackl,[5] 1991	21	Acute phase	>6 or <6	Basal, TRH + arginine stimulation	↑Cortisol	Impaired response to arginine stimulation	↑T4	N/A	Low
Della Corte,[10] 1998	22	Day 1–5	4–8	Basal, GHRH + TRH Stimulation	↓ Cortisol day 2–7	↑IGF-1 day 7 + 15 Exaggerated GH response to GHRH	TSH + T4 normal T3 low	N/A	Unchanged
Cernak,[8] 1999	18/31	7 days	13–15 ($n = 8$) Closed injury	Basal	↑ Cortisol day 1 + 2	N/A	↑TSH day 1–3 ↑T3 day 1,5,7, T4 unchanged	↓Testosterone	N/A
			4–6 ($n = 10$) Penetrating Injury	Basal	↓ Cortisol day 1–3, ↑ Cortisol day 5–7	N/A	↓TSH day 1–7, ↓T3 day 1–7, T4 unchanged	↓Testosterone day 1–7	N/A
Agha,[1] 2004	50	12 days Median	3–13	Basal + GST	16% deficient	18% deficient	2% deficient	80% deficient	52% high
Cohan,[6] 2005	80	1–9 days	3–13	ACTH + Cortisol	53% insufficient	N/A	N/A	N/A	N/A
Tanriverdi,[7] 2006	52	24 h	3–15	Basal	9.8% deficient	20.4% deficient	5.8% deficient	41.6% deficient	12% high
Present study	**30**	**24 h**	**<13**	**Basal**	**High in 80%, low in 3.3%**	**High in 26.7%**	**High in 3.3%, low in 13.3%**	**High in 4.3%, low in 39.2%**	**High in 26.7%, low in 3.3%**

ACTH, adrenocorticotropin hormone; GCS, Glasgow coma scale; GH, growth hormone; GHRH, growth-hormone-releasing hormone; GST, glucagon stimulation test; IGF-1, insulin like growth factor 1; N/A, not available; T3, triiodothyronine; T4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

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patients were males, and sustained injury due to road traffic accidents. Hormonal evaluation revealed that 80% of the patients had a higher than normal cortisol values against 3.3% of the patients with a low cortisol level (reference 5–23 μg/dl). Other hormonal levels were also found to be abnormal (Table 3). Six patients expired and all of them had a poor GCS (mean 4.8 ± 0.9) at presentation.

Univariate analysis revealed that infarct seen on CT scan, and GCS at presentation had significant influence ($p < .05$) on mortality. Intracranial hematoma, and high cortisol level showed a trend towards significance ($p = 0.094$ and 0.097 respectively) on mortality. However the true significance of these findings could not be statistically ascertained as multivariate analysis was not possible because of less number of patients available.

4. Discussion

There is little agreement among the studies about the nature of neuroendocrine changes post-TBI and these variations may reflect differences in patient selection, severity of injury, study design, and methodology, and timing of the assessment. Most studies of hormonal evaluation in acute stage had patients with severe TBI.[1,4–7] Most of our patients also had severe TBI. Hormonal analysis of our patients and their comparison with other studies in the acute setting is shown in Table 3.

In acute setting Cernak, et al noted that serum testosterone correlated with severity of injury[8]; however, this was not supported by the findings of the study by Lee, et al.[9] Hackl, et al reported that impaired GH response to arginine stimulation, and a flat TSH response to thyrotropin-releasing hormone (TRH) were associated with poor outcome,[5] whereas the study by Della Corte, et al showed a paradoxical rise in growth hormone response to TRH, which predicted poor outcome.[10] Behan, et al noted that serum prolactin correlated negatively with Glasgow coma scale (GCS) scores.[11] In our study none of the hormones studied except for serum cortisol showed any significant correlation with the severity of injury or mortality. Dynamic test are neither feasible, nor necessary in acute setting, hence we did not perform these tests.[11]

Elevated cortisol is a well know stress phenomenon, but there is no normative data available on cortisol levels in TBI, hence we used laboratory reference to identify abnormal cortisol levels. Cohan, et al, used cutoff of 15th centlie (<15 μg/dl), data derived from extracranial injuries, to define hypocortisolism in acute TBI.[6] Studies on cortisol levels after TBI have shown conflicting results. Cohan, et al, found that low cortisol levels (<15 μg/dl) were associated with higher injury severity scores and early ischemic insults.[6] We used <5 μg/dl as cutoff, and had only one patient with low cortisol levels. In our study elevated cortisol levels showed a paradoxical trend towards significance for mortality, as opposed to some other studies.[1,7] Tanriverdi, et al found a positive correlation between severity of injury and cortisol levels in mild and moderate TBI, but this was not demonstrable in patients with severe TBI.[12] However, we found positive correlation of raised cortisol with severity of injury. Cemak, et al, noted that serum cortisol was significantly increased after neurotrauma but only up to day two after trauma.[8] This may explain similar findings in our study, as all our samples were collected in the acute setting within the first 24 h of trauma. Feibel, et al,[4] found that patients with elevated intracranial pressure (ICP), and normal brain stem function had persistently elevated cortisol concentrations (15.4 ± 2.6 μg/dl; $p < .001$). They concluded that elevated ICP in the presence of normal brain stem function is a potent stimulus for adrenocortical activation, and that the brain stem is involved in this response. Though ICP was not measured in our study, 29 out of the 30 patients had CT scan findings suggestive of raised intracranial pressure. This may be an explanation of the disproportionately high cortisol levels in our group of patients.

The limitations of our study were less number of patients, lack of subcategorization of severity of TBI, and performance of only basal hormonal levels. Because of lack of adequate funding we could not perform large scale study. However other studies on hormone dysfunction in severe TBI in acute stage have also included only 21–31 patients.[4,5,8,10] Studies with larger number included patients ranging from GCS 3–15.[1,6,7] The second limitation was a subcategorization of severity of TBI, as we had few patients, we did not present results of moderate and severe TBI separately. However in a study including all range of severity of TBI, the authors found a positive correlation between severity of injury and cortisol levels in mild and moderate TBI, but not in patients with severe TBI.[12] Third limitation was lack of dynamic tests, and end organ hormone analysis (e.g. free T3). Dynamic tests definitely improve yield of hormonal deficiency results. These tests are very helpful for detection of subclinical deficiency in patients at follow up. However dynamic test are neither feasible, nor necessary in acute setting, hence we did not perform these tests.[11]

5. Conclusion

Some recent publications have advocated the use of screening for hormonal deficiency in the acute setting, especially cortisol,[6,11] however the present study and other studies are not conclusive for identifying subgroup of patients who are most likely to have this deficit. Some of the abnormalities identified in the various studies are partial deficits, and may be of uncertain clinical significance. The available literature as well as the present study lack statistical strength due to the small number of patients analysed. Further extensive multicentric study with proper patient selection is warranted before these recommendations are accepted in the clinical practice. However, present data clearly demonstrate that pituitary function is disturbed in TBI in the early acute phase, and elevated cortisol may be considered as a marker of severity of injury, besides GCS and CT scan findings.

Conflicts of interest

All authors have none to declare.

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