



Dilemmas in the Management of Acute TBI: A Prospective Observational Study of Anterior Pituitary Dysfunction and Its Correlation with Outcome

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Abstract

Background The frequency and pattern of endocrinal abnormalities among patients with traumatic brain injury occur more frequently than previously suspected.

Objective The aim of this study was to assess anterior pituitary dysfunction in patients with moderate-to-severe traumatic brain injury and outcome after treatment.

Material and Methods One hundred patients with moderate-to-severe head injury presenting within 48 hours of injury were enrolled. Blood samples of all patients were taken for the hormonal assay at second day, at 2 weeks, 1 month, 3 months, and 6 months. Patients were evaluated by Glasgow coma scale (GCS), Glasgow outcome score (GOS), and hormone profile.

Results The median GCS score was 10/15. Forty-four patients were operated and 56 patients were managed medically. Seven operated patients expired; 30 patients had good recovery. In conservative group, 46 patients had good outcome and two patients died. Cortisol and thyroid hormone values were changed prominently, followed by prolactin and growth hormone. On univariate analysis, association of GOS with fT3, fT4, serum prolactin, and serum cortisol was seen. On multivariate analysis, strong correlation of GOS with fT4 values was seen ($p = 0.008$)

Conclusion Most of the hormonal deficiency occurs in immediate phase. Hormonal screening should be done to improve long term outcome.

Keywords

- ▶ traumatic brain injury
- ▶ anterior pituitary dysfunction
- ▶ Glasgow coma scale
- ▶ Glasgow outcome score
- ▶ hormone

Introduction

Traumatic brain injury (TBI) is the most common cause of death and disability in young population living in developing countries. Nearly 180 to 250 persons per 1,00,000 per year

die or are hospitalized due to brain injury.¹ Motor vehicle accidents are the most common cause of TBI and due to increase motor vehicle use incidence is increasing in low- and middle-income countries.² In the course of understanding the underlying mechanism of primary

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and secondary brain damage in acute TBI, some factors are being less focused that have bigger potential in overall neurological severity and outcome of the patient. The neurological outcome and quality of life of patients following TBI could be severely impaired due to hormonal deficiencies. Neuroendocrine abnormalities after TBI are increasingly recognized in recent years due to their potential contribution to morbidity and possible mortality. Various anterior pituitary function abnormalities can cause decreased cardiac function along with increased cardiovascular disease, respiratory compromise, lethargy, fatigue, electrolyte imbalance, diabetes insipidus, and various neuropsychiatric problems.³ In this prospective study, we tried to validate the changes in anterior pituitary hormones following moderate and severe acute TBI and their correlation to neurological outcome.

Patient and Methods

A total of 100 patients with moderate-to-severe acute TBI patients who presented within 48 hours of injury in a tertiary care hospital were included in this study. The severity level of the patients was determined by Glasgow coma scale (GCS). A score of 13 to 15 was considered mild, 9 to 12 moderate, and 8 or less, severe TBI.

Exclusion criteria: Patients with a previous history of endocrine abnormalities or patients having polytrauma, for example, major visceral injury, long bone fracture, and the patients who died within 2 days of admission, were excluded.

Demographic details regarding age and sex of the patients along with clinical features, detailed history, and clinical examination were recorded. The interval between injury and neurological status with deficit was noted. All patients were assessed both clinically and radiologically. A noncontrast computed tomography scan (NCCT) head of each patient was done and managed either by surgical or conservative method as per standard evidence-based guidelines. Patients were evaluated by GCS, NCCT head scan, and anterior pituitary hormone profile at second day. Each patient was followed up at 2 weeks, 1 month, 3 months, and 6 months. Outcome was assessed by using Glasgow outcome score (GOS) at the end of second week and 6 months. Blood samples were primarily collected at around 11 AM in all the enrolled subjects on second day, at 2 weeks, 1 month, 3 months, and 6 months. Upon collection, each sample was centrifuged within 2 hours, aliquoted in polypropylene cryovials, and stored at -40°C until the time of hormonal assay and immunoassay was done. All hormone levels were measured using immunoassay kits from Johnson & Johnson. All data was analyzed at the end of study to derive all important variables that are related to the case and their effect on the outcome.

Statistical analysis: Statistical Package for the Social Sciences SPSS 20.0 Package (Chicago, Illinois, United States) was used. Normally distributed values between two variables were compared by unpaired *t*-test. Correlations were measured with Spearman's correlations coefficient

value. A *p*-value less than 0.05 was considered statistically significant. A logistic regression model was used to determine which variables independently predicted the good outcome.

Results

The median GCS score among the TBI patient was 10/15. TBI in the patients is mainly caused by road traffic accident 72 patients, followed by fall from height in 25 patients and assault in three patients.

The most common (94%) associated intracranial finding in NCCT head of TBI patients was brain edema followed by parenchymal contusion (90%), subdural hematoma (34%), pneumocephalus (2%), subarachnoid hemorrhage (7%), and the rest 11% were having diffuse axonal injury. Most common brain contusion was multiple contusions followed by frontal/bifrontal contusions. Nineteen patients (19%) had fracture of parietal bone, followed by frontal bone fracture in 18 patients (18%), temporal bone fracture in 15 patients (15%), and occipital bone fracture in three patients (3%).

Course in hospital: Forty-four patients (44%) were operated and 56 patients (56%) were managed medically. Seven operated patients expired; 30 patients had good recovery and GOS was 5 in 12 patients, 4 in 18 patients, 3 in 4 patients, and 2 in three patients. In conservative group, 29 patients had GOS of 5, 17 patients had GOS of 4, while three patients had GOS of 3. Four patients had GOS of 4 and two died, with GOS score of 1.

Hospital stay: Average stay in hospital was 9.79 days. It was significantly increased in severe head injury (19.04 days) as compared with moderate head injury group ($p = 0.002$).

Hormonal Value

Cortisol and thyroid hormone values were changed prominently, followed by changes in prolactin and growth hormone. On day 2, 90 patients had normal T3, 92 patients had normal T4, and 74 patients had normal thyroid-stimulating hormone (TSH). Low T3 and T4 values were found in ten and eight patients, respectively. After 6 months, 29 patients had low T3, while only 10 patients had low T4. By 6 months, 75 patients (82%) had TSH value in normal range. Six percent patients had low TSH value but experienced gradual improvement and only one had low TSH at 6 months. It was high in 15 patients at 6 months (16.48%). Free T4 (fT4) was normal in 92 patients (92%) at 2nd day and at 6 months fT4 was normal in 78 patients (85.71%). It was low in 8 (8%) on second day and further deteriorated in 2 and was low in 10 patients at 6 months (10.98%). FT3 was normal in 90 patients (90%) on 2nd day but it dipped further and was normal only in 62 patients (68.12%) at 6 months. It was low in 10 patients initially on 2nd day but on follow-up new patients developed hypothyroidism and was low in 29 patients (31.86%) at 6 months. It was also transiently raised in two patients. So, more patients were hypothyroid at 6 months (29% low fT3) in comparison to on 2nd day values (10% had low T3).

Serum prolactin: It was normal in 85 patients and high in 15 patients initially (2nd day) and was normal in 73 patients

(80.21%) after 6 months. It was high in 11 patients (12.08%) at 6 months.

Growth hormone: Growth hormone was normal in 91 patients (91%) on 2nd day and was normal in 86 patients (94.50%) after 6 months. It was low in nine patients on 2nd day and improved in four and was still low in five patients (5.49%) after 6 months.

Serum cortisol: Serum cortisol was most common hormone to rise in patients with moderate to severe TBI. Thirty-two patients (32%) showed hypercortisolism on 2nd day of head injury. The serum cortisol level normalized in most of the patients over the 6 months follow-up

(68–80.21%). It was high in 17 patients at 6 months follow-up (18.68%).

Follicle-stimulating hormone and luteinizing hormone (FSH and LH): FSH was normal in 95 patients (95%) on 2nd day, and at 6 months, it was normal in 87 patients (95.60%). It was low in two patients on 2nd day and remained so at 6 months. On 2nd day, three patients were having high FSH. At 6 months, two patients had high FSH. LH was normal on second day in 94 patients (94%), and at six months 84 patients (92.30%) had normal values. Five patients (5%) were having low LH on 2nd day. One patient had high LH value on 2nd day. At 6 months, four patients had low LH and three patients had high LH ▶ **Table 1.**

Table 1 Anterior pituitary hormone profile over 6 months

Hormone	Day 2 n = 100	Day 14 n = 93 (7 died)	One month n = 91 (9 died)	Three months n = 91 (9 died)	Six months n = 91 (9 died)
TSH (0.465–4.68 mIU/L)					
Normal	74%	74 (79.56%)	74 (81.31%)	76 (83.51%)	75 (82.41%)
Low	6%	2 (2.18%)	2 (2.19%)	1 (1.09%)	1 (1.09%)
High	20%	17 (18.27%)	15 (16.48%)	14 (15.38%)	15 (16.48%)
Free T4 (0.78–2.19 ng/dL)					
Normal	92%	72 (77.41%)	80 (87.92%)	75 (82.42%)	78 (85.71%)
Low	8%	16 (17.20%)	10 (10.98%)	10 (10.98%)	10 (10.98%)
High	0	5 (5.37%)	1 (1.09%)	6 (6.59%)	3 (3.29%)
Free T3 (2.77–5.27 pg/mL)					
Normal	90%	85 (91.39%)	69 (75.82%)	63 (82.42%)	62 (68.13%)
Low	10%	15 (16.12%)	20 (21.97%)	27 (29.67%)	29 (31.86%)
High	0	0	2 (2.17%)	1 (1.09%)	0
Cortisol (123–626 nmol/L)					
Normal	68%	68 (73.12%)	66 (72.52%)	71 (78.02%)	73 (80.21%)
Low	0	0	1 (1.07%)	1 (1.07%)	1 (1.07%)
High	32%	25 (26.88%)	24 (26.37%)	19 (20.87%)	17 (18.68%)
Prolactin (3–18.6 ng/mL)					
Normal	85%	84 (90.32%)	81 (89.01%)	81 (89.01%)	73 (80.21%)
Low	0	0	0	0	0
High	15%	9 (9.67%)	10 (10.98%)	10 (10.98%)	11 (12.09%)
GH (1–16.4 µg/dL)					
Normal	91%	88 (94.62%)	86 (94.50%)	87 (95.61%)	86 (94.50%)
Low	0	0	0	0	0
High	9%	5 (5.37%)	5 (5.49%)	4 (4.39%)	5 (5.49%)
FSH (1.55–9.74 mIU/mL)					
Normal	95%	91 (97.85%)	87 (95.60%)	84 (92.34%)	87 (95.60%)
Low	2%	1 (1.09%)	1 (1.09%)	2 (2.19%)	2 (2.19%)
High	3%	1 (1.09%)	3 (3.3%)	5 (5.49%)	2 (2.19%)
LH (1.8–7.8 mIU/mL)					
Normal	94%	85 (91.39%)	88 (96.60%)	88 (96.60%)	84 (92.30%)
Low	5%	7 (7.52%)	2 (2.19%)	2 (2.19%)	4 (4.49%)
High	1%	1 (1.09%)	1 (1.07%)	1 (1.07%)	3 (3.39%)

Abbreviations: FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

Gonadal Hormones

Serum Testosterone (Total)

On 2nd day, 80 patients (89.89%) had normal value and nine patients (10.11%) had low values. While at 6 months, 73 patients (89.02%) had normal values and nine patients (10.98%) had low values.

Serum estrogen and progesterone: Estrogen was normal in all 11 patients initially but later one patient developed hypogonadism at 2 weeks but improved at the end of study at 6 months. Progesterone was normal in 10 out of 11 patients on 2nd day and one patient had low value that persisted at 6 months of study.

Outcome: Out of total 100 patients, nine patients had died (9%), seven within 2 weeks and another two patients within a month. Among mortalities, two patients were females and seven patients were males. GOS was 5 in 41 patients, 4 in 35 patients, 3 in 8 patients, and 2 in 7 patients, and 9 patients had score of 1, who died. ► **Tables 2, 3, and 4**

Discussion

Hypothyroidism following TBI was first described in 1918.⁴ It may be partial or complete and reports show that 25 to 50% of patients have some degree of pituitary dysfunction.⁵⁻⁹ Following trauma there is a biphasic pattern of metabolic responses during acute (within 24 hours post injury) and subacute periods (several days after injury).¹⁰ This biphasic response is described as “ebb” and a “flow.” Ebb phase is caused by sympathoadrenal storm that consists of decrease in overall energy expenditure of the body and brain tries to maintain homeostasis by altering normal tissue perfusion. Then “flow” phase occurs wherein substrates are provided for trauma repair by various catabolic processes.¹¹ Mostly elevated anterior pituitary hormones are observed in acute/subacute periods. The underlying mechanism of posttraumatic pituitary damage is complex. Fractures

involving skull base along with sella turcica can cause focal damage and can lead to hypopituitarism. Shearing forces can directly injure the pituitary gland or infundibulum.¹² Swelling of pituitary following TBI leads to compression of the gland. The gland lies in bony compartment of sella and is roofed by diaphragm sella making it vulnerable for injury in moderate and severe TBI.¹³ Post-head injury ischemic event may lead to hypopituitarism. Hypophyseal-portal circulation supplies anterior lobe of pituitary through long portal vessels that run along infundibulum to anterior pituitary and can be damaged from hypertension/hypotension, mechanical forces and edema.^{14,15}

Prolactin

Prolactin is the only pituitary hormone that is under hypothalamic inhibition.¹⁶ Lactotrophs that secrete prolactin are usually located in the periphery of the gland so that it can escape destruction by anterior pituitary necrosis.¹⁷ In our study, hyperprolactinemia was seen in 15 patients at day 2 of head injury that decreased to 11 patients at 6 months follow-up. Lieberman et al⁶ found 10% patients had hyperprolactinemia. Prasanna et al¹⁸ found increased prolactin in 65 patients. Prolactin level was low in conservative group as compared with operated group and was high in severe TBI patients. Overall negative correlation was found with GOS at admission and also at 6 months.

Cortisol

Following trauma, adrenocorticotropic hormone release leads to hypercortisolism. This is a response to favor the body metabolically while healing and recovery occur. It improves hemodynamic status and protects the body against excessive inflammatory or immune responses.^{19,20} In this study, 32 patients had hypercortisolism 2 days after TBI, which reduced to 17 patients at 6 months follow-up.

Table 2 Anterior pituitary gonadal hormone profile over 6 months

Hormone	Day 2 n = 100	Day 14 n = 93 (7 died)	One month n = 91 (9 died)	Three months n = 91 (9 died)	Six months n = 91 (9 died)
Serum testosterone (total)	(n = 89)	(n = 84)	(n = 82)	(n = 82)	(n = 82)
Normal	80 (89.89%)	79 (94.05%)	75 (91.47%)	75 (91.47%)	73 (89.02%)
Low	9 (10.11%)	5 (5.96%)	7 (8.54%)	7 (8.54%)	9 (10.98%)
High	0	0	0	0	0
Estrogen	(n = 11)	(n = 9)	(n = 9)	(n = 9)	(n = 9)
Normal	11 (100%)	8 (88.90%)	8 (88.90%)	8 (88.90%)	9 (100%)
Low	0	1 (11.11%)	1 (11.11%)	1 (11.11%)	0
High	0	0	0	0	0
Progesterone	(n = 11)	(n = 9)	(n = 9)	(n = 9)	(n = 9)
Normal	10 (90.09%)	8 (88.90%)	9 (100%)	8 (88.90%)	8 (88.90%)
Low	1 (9.09%)	1 (11.11%)	0	1 (11.11%)	1 (11.11%)
High	0	0	0	0	0

Table 4 Comparison between operated and conservative group

Criterion	Operated (n = 44) (mean values) Group 1				Conservative (n = 56) (mean values) Group 2			
	1 Operated	2 Conservative	1 Operated	2 Conservative	1 Operated	2 Conservative	1 Operated	2 Conservative
Age	Year 39.18 ± 19.56				Year 35.4 ± 17.11			
Stay in hospital	Days 6.1 ± 8.803				Days 14.45 ± 18.561			
Group	1 Operated	2 Conservative	1 Operated	2 Conservative	1 Operated	2 Conservative	1 Operated	2 Conservative
TSH	2nd Day				3 Months			
“p”-Value	0.056				0.904			
Free T4	0.056				0.205			
“p”-Value	0.056				0.205			
Free T3	0.056				0.205			
“p”-Value	0.043				0.147			
FSH	0.043				0.147			
“p”-Value	0.043				0.147			
LH	0.043				0.147			
“p”-Value	0.043				0.147			
Prolactin	0.043				0.147			
“p”-Value	0.043				0.147			
GH	0.043				0.147			
“p”-Value	0.043				0.147			
Cortisol	0.043				0.147			
“p”-Value	0.043				0.147			
Serum testosterone (total)	0.043				0.147			
“p”-Value	0.043				0.147			

Abbreviations: FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

Tandon et al¹⁶ reported increased cortisol level in 66 patients out of 99 patients recruited in their study within 24 hours of head injury that diminished to 2 patients at 6 months follow-up. King et al²¹ reported elevated level of cortisol as late as 4 months after head injury. Cortisol level was more in operated group as compared with conservative group and was statistically significant. Cortisol values were more in severe head injury patients as compared with moderate head injury patients.

Growth Hormone

Somatotrophs produce GH and are present in lateral and peripheral regions of pituitary gland that make them prone to ischemia due to downstream position relative to long portal vessels.^{22,23} In our study, nine patients had low GH at day 2 of head injury and five patients had low GH at 6 months follow-up. GH values were low in conservative group as compared with operative group and was statistically significant. Various authors have different conclusions regarding GH levels following TBI.^{24–28}

Thyroid Profile

In our study, we observed decreasing trend of T3 and T4 levels over the follow-up duration. T3 was low in 29 patients and T4 in 10 patients 6 months post-TBI. TSH was normal in 75 patients, while 15 patients had high TSH and one patient had low TSH at 6 months post-TBI. T3 and T4 values were more in conservative group as compared with operative group. Effect of severe illness on thyroid function was reported by Wartofsky and Burman.²⁹ Tandon et al¹⁶ also observed decreasing trend in T3 and T4 levels.

FSH/LH

No correlation was found between GOS and FSH. Serum LH levels correlated positively with GOS at 3 months and GCS at 2 weeks.

Estrogen/Progesterone

Estrogen was normal in all patients initially, but later one patient had decreased estrogen at 2 weeks, while gradually improved at 6 months. Progesterone was low in one patient on day 2 and it persisted at 6 months follow-up. In our study, univariate analysis showed association of GOS with fT3, fT4, serum prolactin, and serum cortisol. Multivariate analysis showed strong correlation of GOS with fT4 values only ($p = 0.008$).

Conclusion

Hormonal abnormalities are commonly seen after TBI. The levels can fluctuate over 6 months. Hormonal changes can affect recovery of a patient with TBI. Some hormonal disturbances recover spontaneously with time. Early

detection and correction may help in expediting the recovery in these patients.

Conflict of Interest

None declared.

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