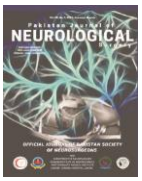

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Original Article (BRAIN)

The Frequency of Low Serum Cortisol Level in Acute Traumatic Brain Injury

Abdul Aziz Khan, Saad Sultan, Baynazir Khan, Attiya Nasir Siddique, Aqsa Shehzadi Rafia Khurshid, Mohammad Waseem, Idrees Ahmad, Sidra Asghar, Khalid Zadran
Department of Neurosurgery, Ayub Medical College and Hospital, Abbottabad, Pakistan

ABSTRACT

Objective: The study focused on evaluating the frequency of low serum cortisol levels in acute traumatic brain injury.

Material and Methods: Patients with Acute Traumatic Brain Injury of both genders between the ages of 2 and 70 years old with a GCS of 12 or below were included. Information including name, age, gender, pregnancy, GCS, serum cortisol level, history of steroid use, and hypothalamic-pituitary dysfunction were all recorded on a predesigned proforma. The results were stratified among age, sex, and GCS concerning outcome variables.

Results: The majority of patients (42%) ranged in age from 26 to 50. Male patients outnumbered female patients (77%). The GCS ranged between 9 and 12 in 63% of cases. Furthermore, 88 percent of patients had cortisol levels greater than 300nm/L. Hypocortisolemia was found in 13 people aged 26 to 50, 12 between the ages of 2 and 25, and only 7 between the ages of 51 and 70. There were 25 males and 7 women in the group. In 86 instances, GCS ranged from 9 to 12, while in 12 individuals, it varied from 3 to 8.

Conclusion: Although the majority of patients recovered, early hypopituitarism was common in severe TBI. It is required to identify concealed pituitary dysfunction in the course of the rehabilitation process of TBI patients.

Keywords: Cortisol, Traumatic Brain Injury, Hypocortisolemia.

Corresponding Author: Abdul Aziz Khan
Ayub Medical College and Hospital, Abbottabad, Pakistan
Email: drabdulazizkhan2121@gmail.com

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INTRODUCTION

Traumatic brain injury is non-degenerative brain damage induced by an external mechanical force, which results in temporary or permanent neurological dysfunction or, impairment of cognitive.[1] TBI is the biggest cause of death and disability among young people, according to a new meta-analysis. Approximately 134 to 600 people per 100,000 are injured each year, which

has a negative impact on the country's economy. [2] Survivors of severe TBI usually experience a slew of physical, endocrine, and neuropsychiatric consequences that necessitate their reliance on others. Among the numerous problems associated with TBI, neuroendocrine hypopituitarism has been found to account for 27 – 47 percent of patients.[14] There is a lack of agreement on conventional diagnostic testing characteristics.[1] TBI is a major source of illness and mortality in both developed and poor nations.[2] According to a recent meta-analysis, traumatic brain injury affects 134 to 600 people per 100,000 people per year, with adult men having the highest prevalence, making it one of the leading causes of mortality and disability, particularly among young guys.[3] TBI-induced hypopituitarism is one of the most underdiagnosed forms of neuroendocrine dysfunction. The frequency of PTHP (post-traumatic hypopituitarism) among long-term TBI survivors ranges from 1 – 83 percent, with a considerable influence on morbidity and death. TBI is a relatively unknown cause of hypopituitarism. Severe TBI has a usually bad prognosis, and the existence of undiagnosed neuroendocrine problems may deteriorate the prognosis even further.[4-6]

The idiopathic etiology of this syndrome, the non-specificity of symptoms, and the absence of a consensus for screening for post-traumatic hypopituitarism have all contributed to the underdiagnosis of this devastating disorder.[2,7] In addition to these, post-traumatic hypopituitarism contributes to the patient's neuropsychiatric symptoms, which have a detrimental influence on the prognosis of traumatic brain damage. The American College of Society of Critical Care Medicine coined the term critical illness-related corticosteroid insufficiency (CIRCI) to describe impairment of the hypothalamic-pituitary-adrenal (HPA) axis at any level, including the hypothalamus, pituitary/adrenal glands, as well as corticosteroid resistance at the peripheral level of target tissues.

CIRCI was proposed to replace "primary/ central and secondary corticosteroid insufficiency" since it described thalamic, pituitary, or adrenal gland dysfunction.[9] Because of the consequences of glucocorticoid insufficiency, the hypothalamic-pituitary-adrenal axis is of particular relevance in the acute setting of traumatic brain injury. Glucocorticoid shortage can result in life-threatening hyponatremia and hypotension that need pressor assistance.[10] CIRCI is distinguished by an excessive and prolonged inflammatory response as well as corticosteroid resistance, resulting in an insufficient corticosteroid response to acute stress.[11-12]

In the case of trauma, at least a plasma cortisol level evaluation should be performed to establish a baseline. Low plasma cortisol levels are linked to an increased risk of death and long-term pituitary impairments. In patients with traumatic brain injury who have low baseline blood cortisol levels, hydrocortisone supplementation should be performed.[13] The current study sought to ascertain the incidence of low blood cortisol levels in acute traumatic brain injury in our setting. The outcome will contribute to the current body of knowledge. Because the evidence will be based on data from the local community, the results may be used by practitioners for evidence-based practice.

MATERIALS AND METHODS

Study Setting

Six-month (19-11-2018 to 19-5-2019) cross-sectional research was carried out in the Department of Neurosurgery, Ayub Medical Institute, Abbottabad.

Sample Size & Sampling Technique

A consecutive (non-probability) sampling was considered and the sample size was calculated from the WHO sample size calculator (CI: 95%),

anticipated population proportion of low cortisol in acute traumatic brain injury 78%, and absolute precision: 5%.

Inclusion Criteria

Patients with Acute traumatic brain injury of both genders between the ages of 2 and 70 years old with a GCS of 12 or below were included.

Exclusion Criteria

Patients having a history of steroid usage in the previous 6 months, as well as pregnant women, were excluded. Patients with hypothalamic-pituitary dysfunction, adrenal insufficiency, or a history of cancer were not included in the study.

Data Collection

The data were collected with the approval of the institutional ethical committee. Patients with TBI were included from the emergency department or out-patient door. Informed consent from all patients was taken. For further examination and assessment, the patients enrolled in Neuro-ICU. The morning serum cortisol levels were measured on day 5 after admission. Information including name, age, gender, pregnancy (for female patients only), GCS, serum cortisol level, history of steroid use, and hypothalamic-pituitary dysfunction were all recorded on a predesigned proforma.

Data Analysis

All data were processed and analyzed on SPSS version 26.0. Mean values were calculated for age, cortisol levels (@ 5-day) & GCS. Frequencies and percentages were used to describe the categorical variables like gender, pregnancy, and hypocortisolemia. The results were stratified among age, sex, and GCS with respect to outcome variables. Post-stratification chi-square test was used.

RESULTS

Age Distribution

Among 264 patients, 98 (37%) were between 2 – 25 years, 111 (42%) were between 26 – 50 years, and 55 (21%) were between 51 – 70 years. The mean age was 30 ± 10.981 years.

Gender Distribution

203 (77%) patients were male and 61 (23%) patients were female patients.

Table 1: Background Clinical Information (n = 264).

Age		
Subcategories	**n**	**%**
2 – 25 years	98	37%
26 – 50 years	111	42%
51 – 70 years	55	21%
Gender		
Male	203	77%
Female	61	23%
GCS Score		
3 – 8	98	37%
9 – 12	166	63%
Serum Cortisol		
More than 300 nm/L.	232	88%
Less than 300 nm/L.	32	12%

Information on GCS

GCS score among 264 patients was analyzed as 98 (37%) patients had GCS score 3 – 8 while 166 (63%) patients had GCS score 9 – 12. The mean GCS score was 9 with SD ± 3.72.

Information on Serum Cortisol Levels

Serum cortisol level among 264 patients was analyzed as 232(88%) patients had serum cortisol levels more than 300 nm/L while 32(12%) patients had serum cortisol levels less than 300 nm/L. The mean serum cortisol level was 289 with SD ± 18.116. The status of hypocortisolemia among 264 patients was analyzed as 32(12%) patients had hypocortisolemia while 232(88%) patients didn't have hypocortisolemia.

Stratification of Hypocortisolemia

Stratification of hypocortisolemia with respect to age, gender, and GCS score is given in **Table 2**. Hypocortisolemia was observed in 13 individuals between the ages of 26 and 50, 12 between the ages of 2 and 25, and only 7 between the ages of 51 and 70. There were 25 men and 7 women among them. GCS ranged from 9 to 12 in 86 cases and 3 – 8 in 12 patients.

Table 2: Hypocortisolemia with respect to age, gender, and GCS score.

	HYPOCORTISOLEMIA (n=264)			
Variables	**Present**	**Absent**	**Chi-Square**	**p-value**
Age				
2 – 25	12	86		0.981
26 – 50	13	98	0.0378	(Insignificant
51 – 70	7	48		result)
Gender				
Male	25	178		0.860
Female	7	54	0.0311	(Insignificant result)
GCS Score				
3 – 8	12	20		0.962
9 – 12	86	146	0.0022	(Insignificant result)

DISCUSSION

The present study sought to determine the prevalence of low blood cortisol levels in patients suffering from severe traumatic brain injury. The majority of patients (42%) were between the ages of 26 and 50. Male patients predominated (77%). In 63 percent of patients, the GCS was between 9 and 12. In addition, 88 percent of patients had cortisol levels higher than 300nm/L.12% of patients had hypocortisolemia while 88% of patients had normal cortisol levels. Contrary to popular belief, critical patients have insufficient cortisol levels in proportion to the severity of the condition, despite an increase in cortisol production in the human body in reaction to stress. Indeed, in some stressful situations, cortisol levels, whether relatively high or normal, may be insufficient for physiological stress, limiting the patient's capacity to cope with any additional stress.[15] TBI suffers from a lack of standardized testing protocols. In the majority of instances, diagnosing adrenal insufficiency (AI) in an intensive care unit (ICU) remains exceedingly challenging.[16-23] AI accounts for around 30 to 50 percent of patients in rehabilitation facilities following a head injury.[22] There is a paucity of research on adrenal function in the first ten days after a stressful event when therapeutic care must be commenced.[22] The vast majority of them have a GH (growth hormone) deficiency, whereas some have another anterior pituitary hormonal deficiency. 24 There is also a strong overlap between chronic TBI sequelae and clinical hypopituitarism features. Changes in the blood-brain barrier, free radical-induced damage, and enhanced apoptosis are some of the pathophysiological pathways that contribute to long-term repercussions following TBI.[25] Hypopituitarism has mild clinical manifestations. Growth hormone (GH), adrenocorticotrophic (ACTH), gonadotropin, and thyroidal insufficiency, as well as diabetes insipidus (DI), have all been observed in the chronic phase following TBI.[26-33]

Our study showed that the mean age was 30 years with SD ± 10.981. Seventy-seven percent of patients were male and 23% of patients were female. Moreover, 12% of patients had hypocortisolemia while 88% of patients didn't have hypocortisolemia. Another research, done by Mirzaie et al. found that the 1-g ACTH stimulation test revealed more instances of AI than the basal blood cortisol level and the 250-g ACTH stimulation test. The test revealed that there was no agreement between these assays. According to the various definitions of AI, the incidence of AI in the first 10 days following traumatic brain

injury ranged from 34% to 82 percent. The prevalence of hypocortisolemia was 10%. Patients identified by the 250-g ACTH stimulation test had a greater prevalence of hypotension and the requirement for vasopressors.[34]

Cortisol levels and vasopressor usage had an inverse connection, as did cortisol levels within 24 hours after damage and etomidate use. High-dose propofol and pentobarbital use was closely linked to reduced cortisol levels.[35] Another research, done by Hari et al, identified hormonal abnormalities in 39 of the 56 patients (70 percent) during the initial examination. Pituitary inadequacies continue after 6 and 12 months in 7 and 8 persons, respectively. The most prevalent diagnosis are hypogonadotropic hypogonadism, hypothyroidism, and growth hormone deficiency. The initial severe TBI and involvement of many hormones suggested long-term hypopituitarism. 36 Chen et al. discovered that 52.2 percent of severe TBI patients had CIRCI, and TBI-associated CIRCI was strongly associated with not only increased mortality but also more frequent complications such as pneumonia and gastrointestinal bleeding, both of which have been linked to poor outcomes in TBI patients.[37]

Bensalah et al, observed a 44.4 percent prevalence of PTHP at 3 months, which dropped to 34.3 percent at 12 months. Our 3-month data agree with those of Bavisetty et al, Aimaretti et al, and Schneider's studies.[38-40] The higher incidence of PTHP in the Bensala et al, study compared to the Klose et al. study (11%) might be explained in part by smaller patient numbers (n = 46) and milder TBI in Klose's trial, in which 22 (50%) of patients had modest CT abnormalities. 41 A research found a 12-month prevalence of PTPH similar to what Schneider et al, Popovic et al and Agha et al, reported.[42-43]

CONCLUSION

Although the majority of patients recovered, early hypopituitarism was common in severe TBI. Evaluation for concealed pituitary dysfunction is required during the rehabilitation of TBI patients. Furthermore, hypocortisolemia was shown to be common in 12% of patients with severe traumatic brain injury.

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Additional Information

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Human Subjects: Consent was obtained by all patients/participants in this study.
Conflicts of Interest:
In compliance with the ICMJE uniform disclosure form, all authors declare the following:
Financial Relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.
Other Relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

AUTHORS CONTRIBUTIONS

Sr.#	Author's Full Name	Intellectual Contribution to Paper in Terms of:
1.	Abdul Aziz Khan, Saad, Baynazir Khan	1. Study design and methodology.
2.	Attiya Nasir Siddique	2. Data calculations.
3.	Rafia Khurshid, Mohammad Waseem	3. Data collection and calculations.
4.	Idrees Ahmad, Aqsa Shehzadi	4. Interpretation of results.
5.	Sidra Asghar	5. Literature review and referencing.
6.	Khalid Zadran	6. Analysis of data.