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Impaired Pituitary Axis Following Traumatic Skull Base Fracture And Associated Brain Injury

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Introduction:
Traumatic brain injury (TBI) is defined as a change in brain function or other evidence of brain pathology caused by external forces and is a well-recognized public health problem worldwide. A substantial number of TBI cases are seen in emergency departments with principal causes including falls, road accidents, assaults and sports-induced concussions. Two important risk factors for TBI are sex (males suffer from TBI 3 times more often than females) and age (people over 65 years old and under 14 year are particularly vulnerable).

The pituitary gland is particularly vulnerable to head trauma due to its anatomical location within the sella turcica , its fragile infundibular hypothalamic structure and its vascular supply. Hypopituitarism is an underdiagnosed sequela of TBI. It was previously thought to be rare, comprising 0.7% of cases of hypopituitarism**[15]**but is increasingly recognized**[16,17].** Understanding its true incidence is difficult as TBI is often not considered by many practitioners in the evaluation of hypopituitarism, even among endocrinologists**[17].** There is significant variability in the timing of presentation with post TBI hypopituitarism ranging from a few days to over forty years though most cases present within the first year**[3-5,20-25].**

Post-traumatic hypopituitarism (PTHP) occurs when the pituitary gland fails to produce one or more hormones due to head injury. TBI patients with PTHP may suffer from a various clinical sequelae, including physical, psychological and cognitive deficits. Symptoms can

present at any time after the trauma and the signs and symptoms of hypopituitarism may be subtle , overlapping with the neurological and psychiatric sequelae of head trauma.

Somatotropic axis**[26-28]** insufficiency is the most common abnormality followed by hypogonadism, hypothyroidism, hypocortisolism and diabetes insipidus. Pituitary dysfunction after a traumatic brain injury is usually transient and may resolve or regain its functional abilities but it can also present clinically or develop years after the initial TBI. TBI has been also linked to impaired quality of life, depression and poor rehabilitation outcome.

Much of the available data is retrospective with only a few prospective series; some combine the two methods. Prospective series also vary in latency between injury and testing. The completeness of the hypothalamic-pituitary axis evaluation also varies among reports with some excluding certain hormones and others only measuring static hormone levels rather than combining static assessments with provocative tests.

Thus, study aimed to evaluate the early and late changes in pituitary hormone levels after TBI and to correlate these changes with outcomes.

Methodology:

This prospective study was conducted on 150 patients presenting in the Trauma Centre of SMS hospital, Jaipur from 1 January 2023 to May 2024.The levels of hormone (GH, TSH, ACTH, FSH, LH, PROLACTIN) were assessed at different intervals: immediately after trauma ,4th day, the 21days and at 3 months post- injury. Other routine investigations and NCCT head scans with sellar cuts were also performed for diagnosing injury. **Inclusion criteria**: All traumatic skull base fracture (with and without brain injury) radiologically proven ,Traumatic sella-turcica or sphenoid bone fractures, History of trauma and consent. **Exclusion criteria:** non traumatic fracture, pituitary diseases, patient with other conditions like micro and macroadenoma that might alter pituitary hormones, non-consenting & uncooperative patients, old traumatic fracture and patients already on hormone therapy.

Patients with a history of trauma were clinically and radiologically evaluated for skull base fracture. CT brain with sellar cuts were performed and evaluated for skull base fractures with and without brain injury or sella-turcica fracture or sphenoid bone injury. Serum samples were collected immediately, on the 4^{th} day, the 21^{st} day and at 3 months after TBI for analysis of growth hormone, thyroid-stimulating hormone, ACTH, FSH, LH and prolactin. Chemiluminescence immunoassay was used for hormone estimation.

Hormonal values are described as mean ± standard deviation and when data was skewed with extreme deviation, median and range were used for analysis. IBM SPSS Statistics 26 was used for data analysis. A two-tailed Student's t-test was applied for continuous data. Skewed data were transformed into logarithmic values and statistical tests were applied to the transformed data. Correlation analyses were made using the Pearson test for continuous data and Spearman's rho test when at least one parameter was ordinal. Factors influencing outcome were explored using logistic regression. A value of $P \leq 0.05$ was considered statistically significant.

Results:

In our study,the mean age of cases was 39.74 years with the majority of cases were in age group ≥51 years (30%) followed by 31-40 (26%). There were 15 females out of 150 cases, with the remaining 135 being males.The cause of trauma in our study was road accidents (65.3%) followed by trauma due to fall from height (24%),assaults (7.33%) and sports -related injuries(3.33%).

Mean Serum TSH at admission was 2.74, followed by 3.11 on the 4^{th} day, 2.07 on the 21^{st} day and 1.95 on the 90^{th} day. On Post-hoc Dunn's test ,we found that mean TSH increased from day-1 to Day-4 (p-value =0.0113).Later, on 21^{st} day ,mean TSH started decreasing up to follow up on the 90^{th} day but this difference at 21^{st} days and 90^{th} day was not statistically significant (p-value= 0.3417). Thus, on admission day, 4.67% had low TSH ,followed by 8% on the 4^{th} day, 9.33% on 21^{st} day and 11.33% on the 90^{th} day. (Fig:1 Table:1).

Table:1

TSH	At Admission	At 4th Day	21st Day	90th Day
Abnormal	7 (4.67%)	12 (8%)	14 (9.33%)	17 (11.33%)
Mean±SD	2.74±1.21	3.11±1.23	2.07±1.15	1.95±1.08

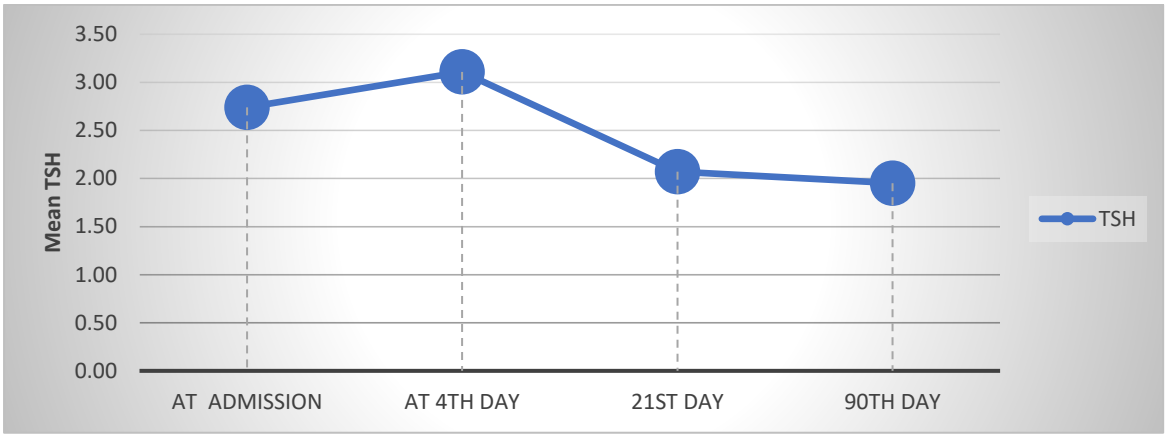


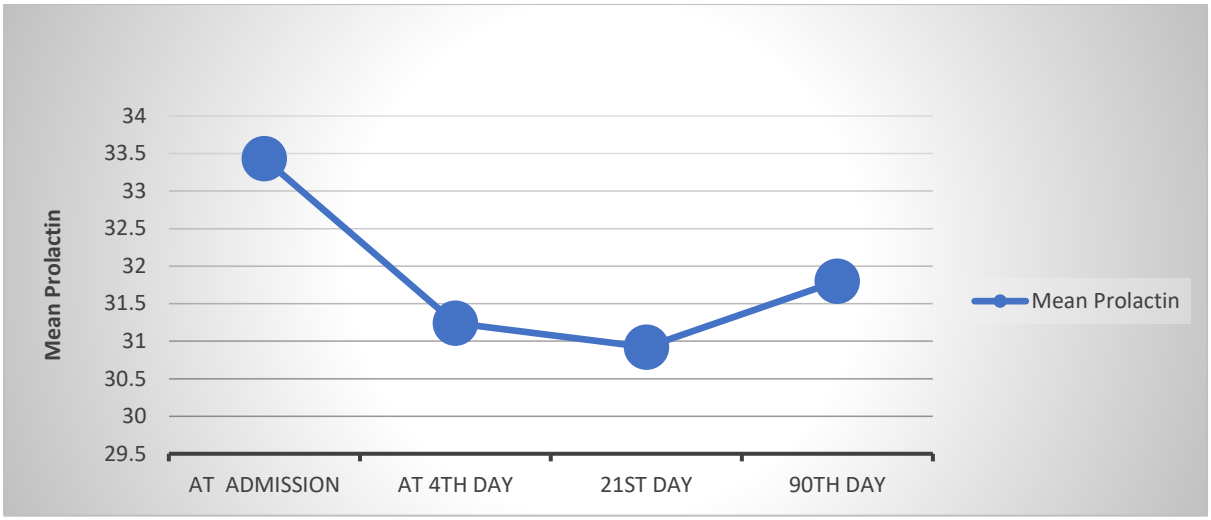
Fig:1

Mean Serum Prolactin at admission was 33.43 followed by 31.24 on the 4th day, 30.92 on the 21st day and 31.80 on the 90th day. On Post-hoc Dunn's test, we found that mean Prolactin decreased from day-1 to Day-4 (p=0.0113). Later, on 21st day, mean Prolactin start increasing up to follow up on 90th day,but this difference at 21st days and 90th day was not statistically significant (p=0.3417). Thus, on admission day, 4.0% had low Prolactin, followed by 6% on 4th day, 6.67% on 21st day and 9.33% on 90th day.(Table:2, Fig:2).

Table:2

Prolactin	At Admission	At 4th Day	21st Day	90th Day
Abnormal	6 (4.0%)	9 (6%)	10 (6.67%)	14 (9.33%)
Mean±SD	33.43±4.10	31.24±3.23	30.92±5.39	31.80±5.76

Fig:2 Prolactin graph



Mean Serum LH and FSH at admission were 13.02 and 12.05,respectively, followed by 11.96 and 11.88 on the 4th day, 12.14 and 10.95 on the 21st day, and 12.93 and 10.12 on the 90th day. On Post-hoc Dunn's test, we found that mean LH and FSH were high on admission day and started decreasing on the 4th day.On follow up on 21st and 90th days, both hormones started to reach a normal level in majority of patients. Thus, on admission day 10% and 9.33% had low LH and FSH,respectively, followed by 12.67% and 12.67 % on the 4th day, 14 and 13.33% on 21st day, and 13.33 and 12% cases on the 90th day. (Table:3,4; Fig:3,4).

Table:3

LH	At Admission	At 4th Day	21st Day	90th Day
Abnormal	15 (10%)	19 (12.67%)	21 (14%)	20 (13.33%)
Mean±SD	13.02±3.94	11.96±3.16	12.14±2.83	12.93±2.52

Table:4

FSH	At Admission	At 4th Day	21st Day	90th Day
Abnormal	14 (9.33%)	19 (12.67%)	20 (13.33%)	18 (12%)
Mean±SD	12.05±2.81	11.88±2.18	10.95±2.09	10.12±1.76

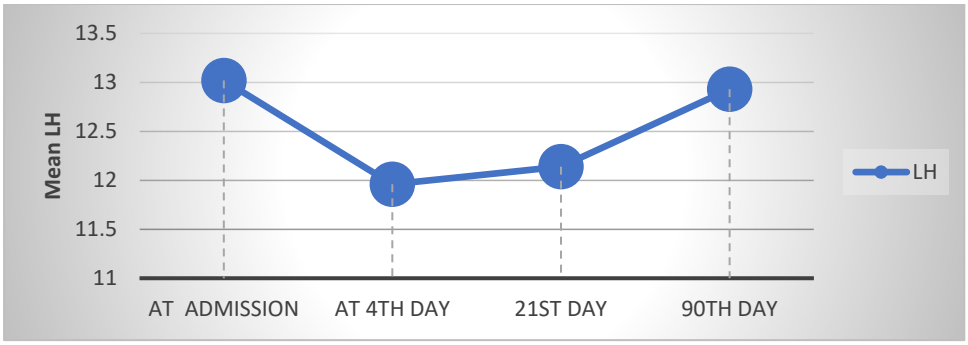


Fig:3

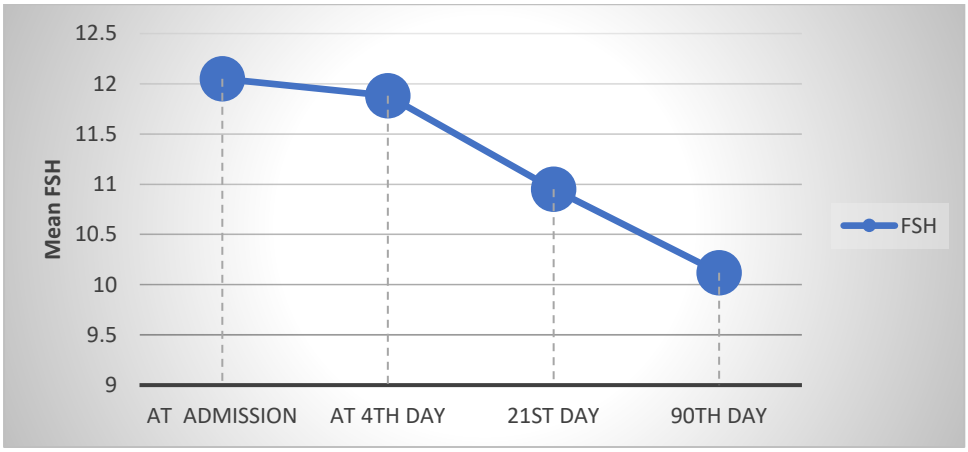


Fig:4

We also found that mean Serum ACTH and GH at admission were 35.73 and 2.37,respectively, followed by 34.20 and 1.13 on the 4th day,32.20 and 1.16 on the 21st day, and 20.51 and 1.14 on the 90th day. On Post-hoc Dunn's test, we found that mean ACTH and GH high on admission day and started decreasing on 4th day. On follow -up on the 21st and 90th days, ACTH levels started to normalize in most patients,but GH levels remained lower. Thus, on admission day, 10% and 8.67 had low ACTH and GH,respectively, followed by 13.33% and 16% on the 4th day, 11.33% and 12% on the 21st day, and 10% and 12.67% on the 90th day. (Table:5,6; Fig:5,6).

Table:5

ACTH	At Admission	At 4th Day	21st Day	90th Day
Abnormal	15 (10%)	20 (13.33%)	17 (11.33%)	15 (10%)
Mean±SD	35.73±11.08	34.20±10.11	32.20±10.21	20.51±10.55

Table:6

GH	At Admission	At 4th Day	21st Day	90th Day
Abnormal	13 (8.67%)	24 (16%)	18 (12%)	19 (12.67%)
Mean±SD	2.37±1.08	1.13±1.02	1.16±0.97	1.14±0.97

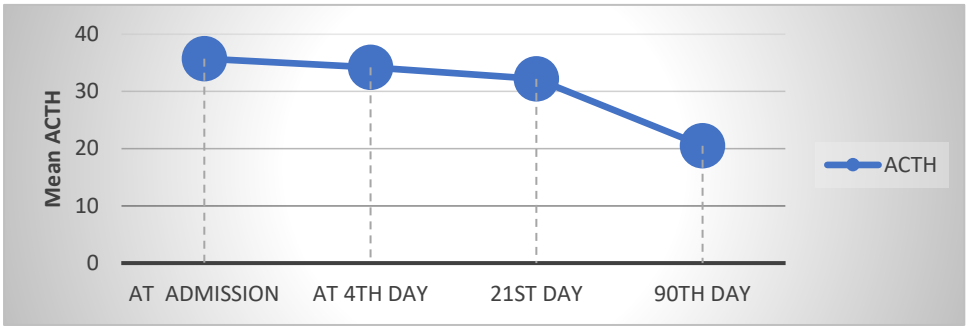


Fig:5

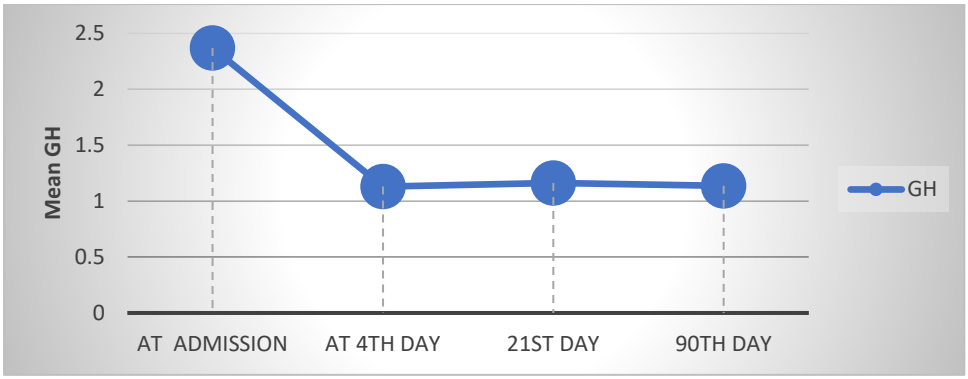


Fig:6

Discussion:

Pituitary insufficiency may have serious consequences and may aggravate the physical and neuropsychiatric morbidity observed after head injury. Patients with TBI may suffer from lethargy, muscle fatigue and poor exercise capacity. Deficiency of GH may lead to reduced lean body mass, decreased exercise capacity, impaired cardiac function, and reduction in bone mineral density. It is found that hypopituitarism may impair recovery from TBI **(Agah et al)[1-5].**Much of the available data is retrospective in nature with only a few prospective series.found that majority of study done so far on endocrine manifestation of traumatic brain injury are retrospective. Presently there is paucity of prospective data on the natural history of post-

traumatic neuroendocrine dysfunctions. There is need to develop appropriate guide- lines for follow-up of suspected cases so that information can lead to timely and appropriate assessment and treatment of hormonal deficits. According to **Agarwal et al** the timing of manifestation of hormonal deficiencies following TBI varies from days to years.

A large number of neuropathological studies established a frequency of 26.4%-86% hypothalamic-pituitary lesions in patients with TBI. 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, and/or pituitary gland, compression from haemorrhage, edema or raised intracranial pressure and vascular injury to the hypothalamus or the pituitary gland. The hypophyseal vessels are anatomically vulnerable to shearing injuries, increased intracranial pressure, anterior base of skull fractures and pituitary ischemia or hemorrhage described as common findings at autopsy.

It was observed that prevalence of GH and ACTH deficiency was 8.67% and10% respectively, on the day of TBI, which increased to 16% and 13.33% on the 4^{th} day. After 21^{st} day of injury, the deficiency of GH and ACTH was found in 12% each and after 3 months, the prevalence of GH and ACTH deficiency was 12.67% and 10% respectively. Our study showed prevalence of GH deficiency similar to other studies but deficiency of ACTH was somewhat lesser in TBI patients. **Agha et al[1-5]** conducted a retrospective study in 2004 and found prevalence of GH deficiency between 8.8% to 10.7% and they reported prevalence of ACTH deficiency in 22.5%. **Kelly et al[6]** who conducted a study on a smaller cohort of 22 patients with moderate or severe TBI. Four patients (18%) had subnormal GH responses but it was not reported how many had clinically significant deficiency. However, Kelly et al reported only one patient having adrenal deficiency. **Lieberman et al [7]** also reported a prevalence of 14% GH deficiency. They also reported that approximately 45% of TBI patients had morning cortisol less than normal range. **Bondanelli et al[7]** also conducted a small cohort study and observed that overall GH response was not significantly different among the TBI group and healthy controls. Actually, **Agha et al[1-5], Kelly et al[6], Lieberman et al[7]** and **Bondanelli et al [8-9]**conducted a retrospective study in which they tried to find the deficiency of GH using Glucagon stimulation test (GST) and Insulin tolerance test (ITT). Adrenal deficiency was evaluated on the basis of Short synacthen test (SST). According to their study if patients failed GST and ITT or SST they were considered GH and ACTH deficient. In Another study conducted by **Agah et al[1-5]** in 2005 reported 18% had growth hormone deficiency in the acute phase, in 6 months 5 patients

recovered function, 2 new deficiencies were detected in 12 months, leaving 5 patients (10%) with GH deficiency. Eight patients (16%) showed subnormal cortisol response in the acute phase, in 6 months 4 patients had recovered and 5 new deficiencies were detected and all 9 patients had persistent abnormalities in 2 months. **Aimaretti et al[12-14]** conducted a study on TBI patients and evaluated the level of different hormones after 3 months and 12 months and they observed that severe GHD was recorded 22.8% of the total TBI. In **Bavisetty et al** study 16% patients had growth hormone deficiency after 3, 6 and 9 month followed by injury. **Tanriverdi et al [11]** study observed that 9.8% had ACTH and 20.4% had GH deficiency at acute phase of TBI and after 12 months follow up 19.2% and 37.7% had ACTH and GH deficiency respectively.

In our study we observed 4.67% had low TSH on day of admission followed by 8% cases on 4^{th} day, 9.33% cases on 21^{st} day and 11.33% cases on 90^{th} day had low serum TSH. **Agah et al[1-5]** observed that TSH deficiency was uncommon. The frequency of TSH deficiency with relation to other anterior pituitary hormone abnormalities is variable. Because the thyrotrophs are located more medially within the adenohypophysis in the protected territory of the short hypophyseal vessels, they may be less susceptible to traumatic injury than the rest of the anterior lobe, which receives its blood supply predominantly from the more vulnerable long hypophyseal vessels. Our results are comparable with those of **Kelly et al[6]** who found only one patient (4.5%) with low T4 and TSH levels, who also showed a blunted response to TRH stimulation. In contrast, Lieberman et al found 11.6% of patients to have low free FT4 without elevated thyrotropin levels, suggesting TSH deficiency. **Leal-Cerro et al[10]** reported 5.8% had TSH deficiency. **Tanriverdi et al[11]** reported 5.8% had TSH deficiency. In **Tanriverdi et al[11]** study initially during acute phase of TBI 5.8% had TSH deficiency and after 12 month follow up same 5.8% had TSH deficiency.

In our study we found that on admission day 4.0% has high Prolactin followed by 6% cases on 4^{th} day, 6.67% cases on 21^{st} day and 9.33% cases on 90^{th} day had high serum Prolactin. In line to our results Agha et al, Kelly et al and Lieberman et al reported hyperprolactinemia in their study. **Aimaretti et al[12-14]** reported mild hyperprolactinemia in 4.2% of TBI.

We reported that on admission day 10% and 9.33 had low LH and FSH followed by 12.67% and 12.67 cases on 4^{th} day, 14 and 13.33% cases on 21^{st} day and 13.33 and 12% cases on 90^{th} day had low serum LH and FSH. **Leal-Cerro et al[10]** reported that 17% patients had

gonadotropin deficiency. **Tanriverdi et al [11]**reported that 41.65 had gonadotropin deficiency at acute phase of TBI and after 12 months 7.7% had deficiency of gonadotropin hormones.

Conclusion:-

An increase in pituitary hormone on day of injury may be attributed to physiological adaptation to acute illness. Post TBI pituitary dysfunction is an entity to recognize with significant clinical relevance. Secondary hypoadrenalism, hypothyroidism and central diabetes insipidus should be treated acutely while deficiencies in growth hormone and gonadotrophic hormones should be initially observed.

Our data show that post-traumatic abnormalities occur early and with high frequency, which may have significant implications for recovery and rehabilitation of TBI patients. After traumatic brain injury, early neuroendocrine abnormalities are sometimes transient, whereas late abnormalities present during the course of rehabilitation. A follow-up strategy with periodic evaluation is a necessary part of the optimal care for patients with traumatic brain injury.

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