

# Traumatic Brain Injury and Pituitary Dysfunction: A Tertiary Care Hospital Based Study.

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## ABSTRACT

**Background:** Traumatic brain injury (TBI), often is associated with lasting functional disability and represents a significant public health problem worldwide. It is one of the leading causes of death in young people in industrialized countries, and patients who survive suffer important clinical consequences, such as long-term cognitive, behavioral, and social defects. **Aims and objectives:** 1) To determine the frequency of acute corticotrophin deficiency in head injury patients with one week of TBI. 2) To determine the incidence of permanent hypopituitarism, 6 months after TBI in Kashmiri population - a potentially high-risk group: SS prone population. 3) To study the factors affecting the development of hypopituitarism after TBI in Kashmiri population. **Methods:** This observational study was jointly carried out by the Departments of Endocrinology and Neurosurgery at the Sher-i-Kashmir Institute of Medical Sciences Srinagar (SKIMS) in collaboration with the Department of Immunology & Molecular Medicine of our institution. After obtaining formal consent, history and examination and baseline investigations, a hormonal profile for evaluation of pituitary dysfunction was taken within one week of presentation and later after 6 months of trauma including stimulation with glucagon injection. **Results:** RTA and fall from height were two common causes of head injury. GCS of the study subjects ranged from 3 to 15 with a median of 11, with 19 subjects (23.5%) having GCS of 8 or less. GCS varied from mild 6.5% to moderate 10.3% and severe 18.3% in terms of APACHE scores. Sick euthyroid syndrome and hypogonadism was seen in 83% and 60.5 % of patients in acute phase which after 6 months period settled at 5.65 and 17.6 % respectively. 52.6 and 18.4 % had one and two axis involvement at time of presentation and 14.3% and 59.5% had one and two axis involvement at 6 months interval of trauma. **Conclusion:** we conclude that hypopituitarism is a clinical condition much more common than previously thought. Considering the epidemiology of TBI and percentage of related hypopituitarism, we are facing a disease that is far more common than perceived one.

**Keywords:** Pituitary Gland, Traumatic Brain Injury.

## INTRODUCTION

Traumatic brain injury (TBI) is often associated with lasting functional disability and represents a significant public health problem worldwide.<sup>[1]</sup> It is one of the leading causes of death in young people in industrialized countries, and patients who survive suffer important clinical consequences, such as long-term cognitive, behavioral, and social defects.<sup>[2-4]</sup> Though first described in 1918, hypopituitarism was considered as a rare consequence of cranial trauma; representing 0.7% of all pituitary insufficiencies.<sup>[5]</sup> Recently, TBI has been demonstrated to be a frequent cause of hypothalamic-pituitary function impairment, contributing to a delayed or hampered recovery in many TBI patients.<sup>[6-8]</sup> Long-term survivors of both TBI and aneurysmal SAH have been found to have a 30% to 55% prevalence of at

least one anterior pituitary deficiency when evaluated up to six years after the initial injury.<sup>[7,16-18]</sup> The potential importance of post traumatic hypopituitarism is increased by the emergence of the syndrome of GH deficiency in adults, which is characterized by decreases in strength, aerobic capacity, and sense of well-being.<sup>[18,19]</sup> Apart from posttraumatic brain injury the other two important causes of hypopituitarism in adult life are pituitary tumors (and/or their treatments) and Postpartum pituitary hypofunction or Sheehan's syndrome. Sheehan's syndrome is widely prevalent in our part of the world.<sup>[20,21]</sup> With improvement in healthcare services here in Kashmir, there has been a palpable decrease in the incidence of Sheehan's syndrome, but we still do see cases of Sheehan's syndrome here every now and then.<sup>[22]</sup> This raises the question whether Kashmiris, a closed community and a distinct ethnic population, are anyways more predisposed to develop hypopituitarism. Given this question, and the paucity of data on hypopituitarism following posttraumatic brain injury in Northern India (where Kashmir Valley is located), we thought it would be interesting to study the prevalence of,

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and the factors predisposing to hypopituitarism after TBI in Kashmiri population.

### Objectives:

To determine the prevalence of acute pituitary insufficiency 0-7 days post injury in patients with TBI. To determine the prevalence of chronic hypopituitarism, six months after TBI in Kashmiri population. To assess the association of hypopituitarism with trauma-related parameters and early post traumatic hormone alterations.

## MATERIALS AND METHODS

### Inclusion criteria:

TBI of all grades reporting with one week of head injury. All selected patients were screened for pituitary dysfunction within one week and at 6 months' interval after TBI for possible hormonal deficiency. Assessment of anterior pituitary function included basal and stimulated hormone evaluation. Patients were initially tested 0-7 days postinjury for measurement of baseline hormone concentrations. Patients were retested at 6 months postinjury; performing a glucagon stimulation testing for measurement of baseline and poststimulatory hormone levels.

### Diagnostic Criteria:

Secondary hypothyroidism was diagnosed in patients with a subnormal serum T4 associated with an inappropriately low TSH. Hypogonadotropic hypogonadism in men was defined as a low serum total testosterone (<250 in men 20-49 years and <180 ng/dl) associated with inappropriately low gonadotropins. Hypogonadotropic hypogonadism in postmenopausal women was defined as inappropriately low gonadotropins for age; and in premenopausal women as presence of amenorrhoea or oligomenorrhoea, associated with persistently low oestradiol and inappropriately low gonadotropins. Hyperprolactinaemia was defined as prolactin above the upper reference limit. Hypothalamic pituitary adrenal deficiency was defined as a basal cortisol <11 µg/dl at presentations (44), and a peak cortisol <14.6 µg/dl (in response to the GST) at followup (45). Growth hormone deficiency (GHD) with Glucagon test was defined in case of peak GH levels <5 µg/mL (22).

## RESULTS

There were 63 males and 18 females involved.

**Table 1: Age and sex distribution of study subjects**

Age group (years)	Male (n=63)	Female (n=18)	Total (n=81)
<20	5 (7.9%)	1 (5.6%)	6 (7.4%)
20 - 29	17 (27.0%)	1 (5.6%)	18 (22.2%)
30 - 39	10 (15.9%)	3 (16.7%)	13 (16.0%)
40 - 49	14 (22.2%)	2 (11.1%)	16 (19.8%)
50 - 59	11 (17.5%)	9 (50.0%)	20 (24.7%)
≥ 60	6 (9.5%)	2 (11.1%)	8 (9.9%)

P> 0.1

### Clinical Presentation

**Table 2: Clinical manifestations of the study population**

Variable	Statistic
Vomiting(N, %)	9, 11.1%
Seizures(N, %)	2, 2.5%
Fracture(N, %)	28, 34.6%
Mean MRS (±SD)	2.98 ±1.15(1 - 5)*
MRS ≥4(N, %)	25, 30.9%
GCS category(N, %)	
• Severe (<=8)	19, 23.5%
• Moderate (9-12)	40, 49.4%
• Mild (13-15)	22, 27.2%
Mean GCS (±SD)	10.5 ±3.14(3 - 15)*
Mean APACHE score	2.8 ±1.28 (1 - 6)*

27% patients had mild GCS, 49% had moderate and 23 % had severe GCS. Five patients (6.6%) had thyroid function test (TFT) pattern mimicking central hypothyroidism whereas the most common abnormality in TFT was mimicking a sick-euthyroid-syndrome (SES) pattern, observed in 83%. Hyperprolactinemia was observed in 8.1%, gonadotroph deficiency in 60.5% and relative corticotroph deficiency in 17.1% (Table 3). Severity of the head injury in terms of GCS and APACHE score significantly correlated with presence of SES and the functional hypogonadism (in males) observed above. Fifty-four (52.6%) of subjects had one or more and 14 (18.4%) patients had two or more pituitary axes affection while as two subjects had three or more axes involvement [Table 3]. As is known in literature, most common axis involvement in the acute phase was that of gonadotrophs, observed in 46 of 76 subjects (60.5%)

**Table 3: Trophic hormone abnormalities observed in base line investigations**

Trophic hormone abnormality	n / N	percent	95% C.I.
≥1 axis	54 / 76	71.05%	59.51% - 80.89%
≥2 axes	14 / 76	18.42%	10.45% - 28.97%
≥3 axes	2 / 76	2.63 %	0.32% - 9.18%
Hyperprolactinemia	6 / 74	8.11 %	3.03% - 16.82%
Central hypothyroidism	5 / 76	6.58 %	2.17% - 14.69%
Gonadotroph deficiency	46 / 76	60.53 %	48.65% - 71.56%
Corticotroph deficiency	13 / 76	17.11%	9.43% - 27.47%

Follow-up: Of the 81 study subjects initially recruited 79 could be contacted of whom 42 reported for repeat testing. As show in the table, 16 patients died during the study period giving a mortality rate of 20.3%. Of these 16 patients, 9 died in the acute phase of TBI in the hospital. Mortality significantly correlated with the severity of TBI.

### Re-evaluation at 6-months

Of the 81 study subjects initially recruited, 42 followed for dynamic hormone testing and thus could be evaluated for presence of hypopituitarism.

**Table 4: Pituitary axes affection in the study subjects, 6-months post TBI**

	n/N	Percent	95% C.I.
Thyrotroph deficiency	2 / 36	5.56%	0.68% – 18.66%
Lactotroph deficiency	6 / 34	17.65%	6.76% – 34.53%
Somatotroph deficiency	25 / 42	59.52%	43.28% – 74.37%
Gonadotroph deficiency	6 / 34	17.65%	6.76% – 34.53%
Corticotroph deficiency	26 / 42	61.90%	45.64% – 76.43%
One or more axis affection	31 / 42	73.81%	57.96% – 86.14%
Two or more axes affection	25 / 42	59.52%	43.28% – 74.37%
Three or more axes affection	8 / 42	19.05%	8.60% – 34.12%

The two most common axes involved at 6 months interval was corticotroph (61.9%) and somatotroph involvement (59.5%) which was followed by gonadotroph and lactotroph (17.6%) and thyrotroph (5.6%) involvement [Table 4]. One or more axis was involved in 73.8% of patients and two or more axes were involved in 59.5% while as 19% patients had 3 or more axes involved.

## DISCUSSION

Though often underdiagnosed neuroendocrine dysfunction particularly TBI-mediated hypopituitarism has long been recognized as a consequence of TBI.<sup>[5,8,9]</sup> But when health resources of any population of a developing country like ours are limited, screening every patient who undergoes any head trauma for hypopituitarism may not be worthwhile. Therefore, the most important aspect concerning the diagnosis of TBI associated hypopituitarism is to define the conditions related to an increased risk of hypopituitarism, the time interval from TBI when it is best to evaluate and the endocrine test that should be performed in such cases. This study was done to determine the prevalence of acute- (0-7 days postinjury) and chronic-hypopituitarism (6 months post TBI) in Kashmiri population, and to assess the association of hypopituitarism with trauma-related parameters. Biochemical changes mimicking hypopituitarism in the early post-traumatic phase observed in 71% of patients is consistent with results of many other studies.<sup>[26,27]</sup> Six months post-traumatically chronic hypopituitarism in the form of one or more axes affection was observed in 73.8% (95% CI, 58.0–86.1), whereas 25 (59.5%) patients had affection of two or more axes. Two commonest pituitary axes affections were that of corticotroph insufficiency in 26 (61%) and somatotroph insufficiency in 25 (59.5%) subjects. Whereas hormone deficits had recovered in 8 patients 6 months' post-injury, new multiple hormone deficits had appeared in 22 patients. This high prevalence of pituitary dysfunction at re-evaluation at six months

post TBI in our study is sharp contrast with the results of similar studies. Whereas Klose et al,<sup>[18]</sup> reported anterior pituitary deficiencies in 6 of the 46 (13%) patients three months post-traumatically, the Indian study reported pituitary dysfunction in 7 of the 41 (17%) patients at 6 months post-injury. In the early post traumatic period there are often hormonal changes that mimic pituitary dysfunction.<sup>[18]</sup> This is included in the physiological response to acute and critical illness, which comprises hormonal changes similar to growth hormone deficiency (GHD), central hypogonadism and hypothyroidism.<sup>[20]</sup> Five of our patients (6.6%) had thyroid function test (TFT) pattern mimicking central hypothyroidism in the acute phase of TBI. However, the most common form of TFT abnormality observed was in the form of sick-euthyroid-syndrome (SES) in 83% of our cases. Other pituitary axes affection in acute phase included hyperprolactinemia in 8.1%, gonadotroph deficiency in 60.5% and relative corticotroph insufficiency in 17.2% cases. All recent studies have reported adrenal insufficiency in acute post injury phase though of varying proportions. In one study,<sup>[15]</sup> adrenal insufficiency was reported in 16% which is similar to ours, but others have reported frequency of adrenal insufficiency varying from 9.8% to 53%.<sup>[29,30]</sup> In our study, serum prolactin concentrations were elevated in only 8.1% of cases, all of whom had moderate to severe head injury, while in other moderate to severe head injury patients there was no abnormality detected in prolactin levels. Similarly, many studies found low testosterone in acute phase indicating suppression of HPG axis that has been related to severity of head injury.<sup>[15]</sup> The evidence related to prevalence of pituitary dysfunction in recovery phase is also varied. Current evidence shows that there is high risk of hypopituitarism after TBI. The exact timing of development cannot be predicted but it has been suggested to have regular assessment of pituitary function at least up to one year after TBI.<sup>[23]</sup> In our study with 81 subjects initially recruited, 42 were available for dynamic testing at 6 months' interval post TBI; 5.6% patients had thyrotroph deficiency, while as 6 (17.65%) patients had lactotroph deficiency. As has been reported in literature GHD was highly prevalent with 59.5% of subjects having GHD. Pituitary dysfunction with at least one hormonal abnormality was seen in 73.8% of patients. One fifth of our patients (8 out of 42) who were tested 6-months post-TBI, had three or more axes affection. The ITT is regarded as potentially dangerous because of the risk of seizures in the acute post-TBI period, and the short synacthen test may give false-normal cortisol responses as there would not have been sufficient time following TBI for the development of adrenal atrophy. For these reasons, we used the GST. This test has been shown to be a reliable alternative to the ITT.<sup>[29]</sup> The question postulated in the beginning that whether our

population where Sheehan's syndrome is highly prevalent is at higher risk of developing hypopituitarism following head trauma seems quite possible in view of high percentage of patients developing hypopituitarism.

## CONCLUSION

In the end, we conclude that hypopituitarism is a clinical condition much more common than previously thought. Considering the epidemiology of TBI and percentage of related hypopituitarism, we are facing a disease that is far more common than perceived one. As such it is recommended that re-testing be done at specific intervals so that actual deficits are seen and accordingly treated. Publication of more studies to create more awareness and remind physicians of prevalence of hypopituitarism is highly warranted.

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