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PREVALENCE OF PITUITARY DYSFUNCTION IN MODERATE-TO-SEVERE TRAUMATIC BRAIN INJURY IN ADULTS: A PROSPECTIVE STUDY.

Neurosurgery

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ABSTRACT

Background: Traumatic brain injury (TBI) is a growing public health problem worldwide and is a leading cause of death and disability. Hormonal alterations leading to post-traumatic pituitary dysfunction (PTPD) usually become apparent in the first hours or days after TBI.In this study, we focused on the prevalence of anterior and posterior pituitary hormonal alterations in the acute and chronic post-TBI period in adults. **Material & Method:** The study design is a prospective study done in RIMS, Ranchi from March 2021-March 2023. Patients of TBI who were fulfilling our inclusion criteria were randomly selected. All pituitary hormonal assessmentwas done both in the acute phase (within 14 days of post-TBI) and chronic phase (1 month, 3 months & 6 months post-TBI). The outcome of patients was analyzed by Modified Rankin Scale. **Result:** Mean ± SD (range) age at the time of TBI in the 80 patients (62 Male:18 Female) was 40.24 ± 16.77 (18-65) years with moderate TBI (GCS 9-12) in 59 (73.75%) and severe TBI (GCS < 8) in 29 (36.25%). RTA was the most frequent cause, occurring in 83.75% of patientsDuring acute phase 16 patients (25%) are found having AI with serum cortisol level 179 ± 98.25nmol/L (< -2 SD). 10 out of 80 patients were found to have GHD (IGF-1 <-2SD) at the end of 3 months & 6 months post-TBI.Presence of DI was seen in 10/80 (12.5% of patients) which is identified around 13 ± 4.52 days. Hypothyroidism was seen in 5% and hypogonadism in 2.5% of study population. **Conclusion:** Despite the publication of several case series, the true incidence of PTHP remains a matter of considerable debate with divergent rates reported between centers. A coordinated approach by neurosurgeons, endocrinologists, and the neurorehabilitation unit is fully recommended to provide adequate care to these patients.

KEYWORDS

Traumatic Brain Injury, Post-traumatic Hypopituitarism, Growth Hormone Deficiency.

INTRODUCTION

Traumatic brain injury (TBI) is a growing public health problem worldwide and is a leading cause of death and disability.[1,2] The causes of TBI include motor vehicles,which are the most common cause, falls, acts of violence, sports-related head traumas and war accidents including blastic brain injuries.[3] More than 90 years ago hypophyseal dysfunction after traumatic brain injury was originally reported by Cyran in 1918.[1] However, the entity received little attention until some years ago when an increasing number of series among adult survivors wanted endocrinologists about the risk for pituitary dysfunction after TBI. The clinical terms regarding severity and phase of TBI are structural imaging, loss of consciousness (LOC), alteration of consciousness (AOC), post traumatic amnesia 24 hr(PTA) and GCS in first 24 hr. In mild TBI structural imaging is normal with 0-30 min LOC, <24hrs of AOC, PTA of 0-1 day and GCS of 13-15 , moderate grade TBI has normal to abnormal structural imaging, with LOC >30mins - <24hr, >24hr of AOC, PTA 1-7days and GCS 9-12. In severe TBI structural imaging is abnormal, with LOC >24hr, AOC > 24hr, PTA > 7 days and GCS <9.

Only case reports and small case series were reported until 2000, but since then pituitary function in TBI victims has been investigated in more detail.[5,6,7] The frequency of hypopituitarism after TBI varies widely amongdifferent studies (15–50% of the patients with TBI in most studies). The estimates of persistent hypopituitarism decreased to 12% if repeated testing is applied. Growth hormone (GH) is the most common hormone lost after TBI, followed by adrenocorticotropic hormone (ACTH), gonadotropins (FSH and LH), and thyroid-stimulating hormone (TSH).[8,9] The underlying mechanisms responsible for pituitary dysfunction after TBI are not entirely clear; however, recent studies have shown that genetic predisposition and autoimmunity may have a role.[10-14] Hypopituitarism following TBI may have a negative impact on page or degree of functional recovery and cognition. What is not clear is whether treatment of hypopituitarism has a beneficial effect on specific function. In this review, the current data related to anterior pituitary dysfunction after TBI in adult patients are updated, and guidelines for the diagnosis, follow-up strategies and therapeutic approaches are reported.

AIMS AND OBJECTIVES

- To estimate the incidence of pituitary dysfunction in acute and chronic phase of post traumatic brain injury in adults.
- To study the predictive factors of post traumatic hypopituitarism.
- To determine relationship between hypopituitarism and findings on NCCT scan of brain after traumatic brain injury.

MATERIALS AND METHODS

Study Setting:
The study is conducted in the Department of Neurosurgery, Rajendra Institute of Medical Sciences, Ranchi.

Study Design: Prospective study.

Study Period: 24 months (March 2021 - March 2023)

Study Population:
Adult patients presented with moderate-to-severe traumatic brain injury in Central Emergency RIMS Hospital,Ranchi fulfilling inclusion and exclusion criteria.

Sample Size: Our study is a prospective study and we have used qualitative variable proportion. So our sample size will be
Formula used: $n = Z^2 x\ p(1-p)$ / $\square^2$
n =sample size
Z = z score which is 1.96 for confidence level 95%
p= expected proportion in population based on previous study (53%)
q= (100-p)
□ = margin of error (5%) So, n=78.14
So, we will take 80 patients as sample size in our study

Inclusion Criteria:
- Age range: >18 years.
- Patient presenting with moderate-to-severe traumatic brain injury.
- Patient diagnosed with traumatic brain injury without any prior endocrine dysfunction.

Exclusion Criteria:
- Patient diagnosed with mild traumatic brain injury.
- Diagnosis of an endocrine dysfunction prior to traumatic brain injury.
- Patient not willing to participate in the study.
- TBI patient in a vegetative state and severely disabled or with low life expectancy.

Statistical Analysis
The data will be entered in MS EXCEL spreadsheet and analysis will be done using Statistical Package for Social Sciences (SPSS) version 21.0. Categorical variables will be presented in number and percentage (%) and continuous variables will be presented as Mean±SD and median. If the normality is rejected then non parametric test will be used.

Statistical tests will be applied as follows-
1. Quantitative variables will be compared using Independent T test/Mann whitney test (when the data set was not normally distributed) between cases and controls.
2. Qualitative variables will be compared using Chi square test/ Fisher's exact test.

A p value of <0.05 will be considered statistically significant

RESULTS
A total of 80 patients with moderate-to-severe TBI met the inclusion criteria and recruited. Five of the 80 families could not be contacted at the end of 6 months and 3 patients had died from late TBI after-effects, leaving 72 families that were contacted. Mean ± SD (range) age at the time of TBI in the 80 patients (62 Male:18 Female) was 40.24 ± 16.77 (18-65) years with moderate TBI (GCS 9-12) in 59 (73.75%) and severe TBI (GCS < 8) in 29 (36.25%). RTA was the most frequent cause, occurring in 83.75% of patients. 61 patients were monitored in the neurosurgical intensive care unit for a mean duration of 15 ± 5.4 days; patients with GCS <9 shows longer stay in ICU as compared to patients with better GCS. 50 patients were mechanically ventilated in the acute phase for a mean duration of 7.1 ± 5 days. In the radiological evaluation,contusion is the most common finding comprising 22.5% and SAH & DAI being the least common (5%). In 47 patients (58.75%) intra cranial surgeries had been performed [25 Decompressive craniectomies; 14 EDH evacuation; 8 (Elevation of depressed fracture +EDH evacuation: DC+EDH).

Pituitary function was evaluated in all 80 patients 48 hrs after admission, 10-14 days, 1 month,3 months and 75 patients at 6 months in post-TBI. Table no. 7 and graph no. 7 shows the incidence of pituitary hormonedeficiency in acute phase of post TBI and Table 8 and graph no.8 shows hypopituitarism in chronic phase.

At 3 months post TBI, PTHP was present in 24/80 (30%) patients, due to isolated GHD in 10, GHD with one or more other pituitary deficiencies in 2 patients. IGF-1 was below the reference range for age for 4 patients, being frankly subnormal (<178 ng/ml), 4 patients with 102 ng/mL (−2.5 SD) and 2 patients with 88 ng/ml (-3.5 SD). Four patients had GHD at 3 months and six patients at 6 months. Out of the 10 patients with GHD at 6 months, AI was found in 5, gonadotrophin deficiency in one and thyroid deficiency in two.

At 3 and 6 months post-TBI, mean (SD) serum cortisol (n = 80) was 407.54 (313.4 ± 124.1) and during acute phase 16 patients (25%) are found having AI with serum cortisol level 179 ± 98.25nmol/L (< -2 SD). Serum cortisol 6 patients out of 16 are found to have normal serum cortisol level at the end of 3 months,one patient at the end of 6 months and one patient died.

In our study,table no. 7 and graph no. 7 shows the presence of DI in 10/80 (12.5% of patients) which is identified around 13 ± 4.52 days. Most of the cases are transient and permanent DI is very rare.

Table no.8 and graph no. 8 shows incidence of hypothyroidism in 4(n=80) 5% of patients two patients showing low fT4 levels for age at assessmentin 3 months post TBI (mean fT4 0.574 ±0.049); normal range 0.9-2.3 ng/dl, associated with normal TSH & fT3 level.In two patients fT4 level remained subnormal on subsequent verification in 6 months post TBI.

FSH & LH are found to be below -2 SD in 2/72 (2.5% of patients) at 6 months post TBI showed in table no. 8 and chart no. 8.

Predictive factors:
As summerised in table no.and graph no.10,11,13 &14 no demographic trauma characteristics was significantly associated with presence or absence of GHD. All 80 patients had cranial CT at the acute phase, immediately within 48 hrs after TBI. Predictive factors of PTHP in bivariate analysis at 3 months were skull base fracture, duration of intubation and initial traumatic imaging according to Marshall stratification, with a significant correlation.In table no. and chart no.14 & 15 severity of brain injury as evaluated by GCS and cerebral edema were seen significantly associated with existence of GHD & AI.

DISCUSSION
TBI is an important public health problem and remains the leading cause of handicap and disability in young adults.[1] Victims are usually young adult males, with RTA and falls being the most frequent causes.[2] The outcome in severe TBI is generally poor, and the presence of neuroendocrine complications may further worsen the prognosis[1]PTHP is now well-recognized as a complication of TBI.

In our study, average age at the time of TBI in the 80 patients (62 Male:18 Female) was 40.24 ± 16.77 (18-65) years with moderate TBI (GCS 9-12) in 59 (73.75%) and severe TBI (GCS < 8) in 29 (36.25%)patients which is closely comparable with **Bensalah et al** (128 M:5 F) 133 patients with average age 32.21 ± 10 (18-65) years with moderate TBI (GCS 8-13) in 100 (75.2%) and severe TBI (GCS < 8) in 33 (24.8%). RTA was the most frequent cause, occurring in 48% of patients.

In the current study, a PTHP prevalence of 32.5% was found at less than 1 month, falling to 30% at 3 and 6 months. Our 3-month data are in keeping with the studies of **Bavisetty et al, Aimaretti et al and Schneider et al**. Reasons for the relatively high frequency of PTHP in our study compared with that of **Klose et al 2007** (11%) could be partly explained by smaller patient numbers (46) showing in table no.1.Several groups have suggested the severity of TBI, based on the admission GCS score, as a predictor of the development of PTHP. **Kelly et al** found that a GCS score of <10 was associated with PTHP.[4] Similarly, in a sample of 104 patients, **Klose et al** reported that 81% of patients who developed PTHP had suffered severe TBI (GCS<9), whereas only 31% of those with normal pituitary function had a history of severe TBI.[19]

A meta-analysis by **Schneider and colleagues** also demonstrated that the highest rate of PTHP (35.5%) occurred in patients with severe TBI, although the prevalence in moderate TBI (10.9%) was actually lower than that in mild TBI (16.8%). In contrast, other groups **(Aimaretti et al, Agha et al)** have found no correlation between post-traumatic pituitary dysfunction and the initial GCS score.

Kelly et al reported that certain imaging findings, such as diffuse brain swelling, on initial CT head scan predicted PTHP[16], while **Schneider et al**, **Klose et al, Bondanelli et al, Bavisetty et a**l found an association between PTHP and diffuse axonal injury or basal skull fracture.[26]However, three other studies (**Aimaretti et al, Agha et al, Bensalah et al)** failed to identify a convincing association between PTHP[14,25,68] Other factors implicated as predisposing to PTHP include hypotension and hypoxia, older age, duration of mechanical ventilation and prolonged intensive care unit $_{stay}$[14,25,68] Hypoadrenalism during the acute phase may have a major impact for the patients, and it is therefore of special clinical interest. **Cohan et al.** [7] reported that 50% of patients with moderate-to-severe TBI had at least transient adrenal insufficiency (AI) in the acute phase (defined by a total cortisol concentration below the 25th percentile of extracranial trauma patients) which was associated with lower blood pressure and higher vasopressor use. They advised that consideration should be given to monitoring of cortisol levels in intubated TBI patients.

In a subsequent study, **Hannon et al.** [8] reported a frequent occurrence of acute hypocortisolaemia and central diabetes insipidus in patients with acute TBI, and they could predict mortality. In 13 of 15 TBI patients who developed hyponatraemia during intensive care, cortisol deficiency was suggested by a total plasma cortisol <300 mmol/L, and hyponatraemia in these patients responded to glucocorticoid treatment.

In study of **Bensalah et al**[68] the prevalence of AI 3 and 12 months post-TBI is relatively high at 31.6% and 25% but these figures conceal much lower values for moderate as opposed to mild AI, with only 5/133 (4%) and 6/116 (5%) patients showing peak cortisol values of <300 nmol/L. In our study prevalence of AI is 20% which is almost similar like in Bensalah having Serum cortisol level of 179 ± 98.25nmol/L at 3 & 6 months post TBI.

Study	N	TBI Severity	Evaluation time	Test	Prevalence of AI in acute phase
Hannon (2013)	100	Moderate to severe	days (1-10) 6 months	days 1,3,5,7 (F) ITT/GST AI if peak F >18.5	days 1-3: 78%
Alavi (2015)	58	Mild, moderate & severe	0-7 days	AI if basal F <7	10.3%
Bensalah (2018)	133-116	Moderate to severe	days 0-7 3 months	AI defined by 3 different cut offs F ≤3, ≤10, ≤15 ITT 93 months)	2.9% F ≤3, 20.2% F≤10, 35.4% F≤15
Present study	80	Moderate to severe	0-14 days 1,3,6 months	AI defined by Cut off F ≤5	20%

In the present study, GHD, hypogonadism and hypothyroidism remain the most commonly identified endocrine deficits in chronic phase, while most studies have found that <10% of patients manifest abnormalities of theACTH-adrenal and thyroid-stimulating hormone (TSH)-thyroid axes in the longer term. **Alavi et al** found that of the 22 patients assessed at >12months following TBI, only two (9.1%) manifested GHD.[51]

The frequency of GH deficiency in our study 3 and 6 months post-TBI was near to 12.5%, similar to the 18% & 12% prevalence reported by **Bensalah**[19] and **Tolli** [12]. The wide variation of 2.6% and 39.7% in GHD prevalence reported in other studies could reflect relatively few centres using the ITT, the gold standard in evaluating growth hormone secretion, different cut-offs for IGF-1, and patient age.

Posterior pituitary dysfunction following TBI is typically transient (<1month duration). In the acute phase, the proportion of patients developing cranial diabetes insipidus (DI) again varies markedly between studies, rangingfrom 2.6% to 51%[21,50,54,57] and perhaps reflecting the inherent difficulties in establishing a firm diagnosis in the presence of confounding factors (eg, vigorous fluid resuscitation, use of hypertonic fluids, etc). **Aimaretti et al** reassessed 100 patients with TBI at 3months' postinjury and found that only 4% had DI[24] ; at 6–9months, 12months and 17months, the percentages of patients with persistent DI were 1.4%–8%,57 58 6%57 and 6.9%, 55 respectively.

CONCLUSION

Traumatic brain injury (TBI) being the growing health problem worlwide is a leading cause of death and disability. A large body of evidence has now demonstrated that patients who suffer TBI are at risk of hypopituitarism. Despite the publication of several case series, the true incidence of PTHP remains a matter of considerable debate with divergent rates reported between centres. The dynamic nature of pituitary function after head injury, the confounders and practical difficulties of studying endocrine function in the early days following major trauma, the limitations of the diagnostic biochemical tools as well as the overlap between post-TBI symptoms and hypopituitarism have posted major challenges to researchers in the field.

The value of routine screening for hypopituitarism during the acute phase after TBI is controversial. However, emerging evidence has shed new light on cortisol dynamics in the days following injury and emphasises the need for clinicians to be vigilant for ACTH deficiency.

Screening for pituitary dysfunction during the chronic recovery phase requires consideration of patient and injury realted factors.Severity of TBI currently provides a reasonable guide as to who requires pituitary evaluation after injury and when to test. Finally, while single (static) blood tests may be used for screening purposes, the limitations of such an approach are well recognised, and definitive investigation frequently requires more complex dynamic hormone testing with interpretation by an experienced endocrinologist.

The possibility that GHD has the potential to impair the health-related quality of life,physical rehabilitation, and functional outcome of the patient leads to the need of systemic assessment of pituitary hormone 12 months after severe TBI.A co-ordinated approach by neurosurgeons, endocrinologists and neurorehabilitation unit is fully recommended to provide adequate care to these patients.

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Limits:

The duration of the study was only 2 years which was not significant for following up the patients.

Only static test for pituitary hormones have been done, not any dynamic tests done which effect the result.

No records of hormonal therapy has been kept of patients who have pituitary dysfunction.

Intraoperative factors like uncontrollable bleeding, bradycardia, hypotension were not taken for the analysis.

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