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Assessment of patterns of pituitary dysfunction after severe traumatic brain injury

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Abstract
Background: Chronic posttraumatic brain injury (TBI) pituitary dysfunction is not a novel concept; nonetheless, it has become increasingly common as a result of increased exposure to its causes, namely traffic accidents, sports-related injuries, falls, and injuries sustained during conflicts. The goal of this study was to identify patterns of pituitary dysfunction following severe traumatic brain injury.
Methodology: A cross-sectional study was conducted by enrolling 200 patients with TBI. Participants were patients having a history of moderate-to-severe TBI at least 3 months before enrolment. Pituitary function test was done for all patients to determine the frequency of pituitary dysfunction, the number of axes deficiencies, and which hormone is mostly affected.
Results: 122 patients had developed pituitary dysfunction after exposure to head trauma, while 78 had not. The most affected hormone by head trauma was the GH in 100 patients (50%), followed by the gonadal axis, TSH, and finally ACTH, 40 (20%), 21(10.5%), and 10 (5%), respectively. We can see that a single hormonal defect was the most prevalent abnormality in 87 (43.5%), followed by two-axis defect in 9 (4.5%) and only 3 patients (1.5%) had suffered from four axes deficiencies.
Conclusion: TBI pituitary dysfunction is more common than expected in the cohort investigated, with a single hormonal deficiency being the most common aberration, with the GH axis being the most impacted.

Keywords: Traumatic brain injury, pituitary dysfunction, hypopituitarism

Introduction
TBI is a serious public health issue, with an annual incidence of 235/10,000 people, and it is the main cause of death and disability in young adults. The development of post-traumatic hypopituitarism (PTH) is a serious consequence following moderate-to-severe head trauma, according to accumulating data over the last decade [1]. The reported frequency of pituitary dysfunction following TBI ranges from 15.4% to 50%, owing to differences in endocrine testing techniques and timing, as well as patient selection. In the chronic period following TBI, a pooled prevalence of 27.5 percent was established in 19 research, and another recent systematic review included 66 studies and 5386 patients revealed a similar 30 percent finding [2].
Pituitary dysfunction after traumatic brain injury (TBI) is not a new concept, especially chronic pituitary dysfunction, which has been recorded with increasing frequency, owing to an increased risk of exposure to its principal causes, namely road traffic accidents (RTA) and wars [3, 4]. TBI is described as "an external force-induced change in brain function or other signs of brain disease." The acute phase of TBI lasts for the first two weeks following the incident, while the chronic phase lasts for three months [4].
RTA is responsible for the majority of the instances, but other prominent causes include a range of sports, including boxing and kickboxing [5, 6]. TBI is exacerbated by war-related head injuries, especially in nations that have recently experienced warfare. The primary ideas explaining post-TBI hypopituitarism include the vascular hypothesis, direct trauma, and the generation of antipituitary antibodies [7, 8].
The present study aimed to evaluate the assessment of patterns of pituitary dysfunction after severe traumatic brain injury.

Methodology
The current study is a cross-sectional study in which 200 participants were included.

Patients who had previously been exposed to TBI were included in the study. According to the degree of the functional neurological loss and the related structural brain damage, TBI can be divided into mild, moderate, and severe categories. It can be acute or chronic in nature, with the acute phase occurring within the first two weeks after the onset of TBI and the chronic phase beginning after the third month.

Posttraumatic amnesia (PTA), which can follow TBI, is the period until the patient regain his full orientation, we have used it as a tool to measure trauma severity, prolonged amnesia for >24 h indicates a severe TBI, while PTA lasting less than a day considered to be moderate.

Inclusion criteria

1. Patients having a history of exposure to head trauma for at least 3 months before enrolment
2. Patient who had suffered from moderate-to-severe TBI.

Exclusion criteria

1. Mild TBI
2. TBI patients in a chronic vegetative state with low life expectancy
3. Patients with a pituitary abnormality on pituitary imaging
4. Patients who were unwilling to participate in the study
5. Patients who had not completed their investigations.

Data collection

After informed verbal consent was taken from the patients anthropometric and clinical data have been taken from each patient in the form of Age, gender, Duration of hospitalization, Site of hospitalization, PTA (for assessment of severity of TBI), Type of trauma and Type of TBI.

Biochemical variables

All patients underwent a thorough history and physical examination to search for any indications or symptoms of an endocrine problem, after which they were scheduled for a pituitary function test on a different day to complete the baseline and dynamic testing. In a fasting condition, 10 ml of blood was obtained from each subject at the work time of 8:30 a.m. Except for plasma adrenocorticotropic hormone (ACTH) samples, which were taken in ethylenediaminetetraacetic acid tubes, all samples were collected in tubes containing clot activator.

All samples were tested in fully automated chemiluminescence immunoassay kits Cobas e411 analyzer series Roche diagnostics, with the exception of insulin like growth factor 1 (IGF 1), which was tested by ELISA (DRG).

Total serum testosterone (males), estradiol (females), prolactin (PRL), luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and total serum thyroxine (TT4) or serum free thyroxine were all measured in the early morning blood samples (FT4).

To test growth hormone (GH), baseline IGF 1 and GH were measured, after which 1 mg of glucagon was injected intramuscularly, and GH was assessed at 2 and 3 hours. If your peak GH level is less than 7.1 ng/mL, you have GH deficiency. A reading of IGF1 less than the typical age reference is considered abnormal. Baseline ACTH and cortisol levels were measured, followed by an ACTH stimulation test in which 250 g of cosyntropin (alpha 1–24 corticotrophin) was administered intramuscularly and cortisol levels were measured immediately before and again after 30, 60, and 90 minutes, in which a peak cortisol level of less than 20 g/dL is considered deficient, and normal or low ACTH (normal value = 10–60 pg/mL) that indicates pituitary adrenal axis deficiency.

Low fT4 (normal value = 0.93–1.7 ng/dL) or low TT4 (normal value = 5.1–14.1 g/dL) concentrations were related with low/normal TSH levels (normal value = 0.27–4.2 IU/ml) to diagnose central hypothyroidism [11]. Low or low normal FSH and LH levels, as well as low testosterone levels, were used to diagnose hypogonadotropic hypogonadism (HH) in men, with a cutoff value of 300 ng/dL [10–40 nmol/L] for testosterone and FSH (1–13 mIU/mL) and LH (1–9 mIU/mL) for FSH and LH, respectively.

Low morning estradiol levels (normal values = 15–300 pg/mL) in the presence of normal or low gonadotropins (FSH = 2–12 mIU/mL [follicular], 20–80 mIU/mL [midcycle], and 0.5–18 mIU/mL [luteal]) are indicative of HH in females.

Statistical analysis

It was done using SPSS software version 20.0 (IBM Corp. Armonk, NY. USA). The categorical variables were expressed as frequency and percentage. The statistical association in relation to categorical variables were interpreted by Chi square test. A $P< 0.05$ was considered statistically significant.

Results

A total of 200 patients has been enrolled in the present study. Table 1 shows the general characteristics of the patients involved in this study. Out of 200 patients, 175 (87.5%) were male and 25 (12.5%) were female. The age distribution at the time of onset of TBI was as follows: patients aged 18 years were 48 (24%), 18 – 44 years were 130 and >45 years were 22 (11%).

RTA was responsible for TBI in 142 patients (71%), while blast and blunt injuries were the causes in 24 (12%) and 34 (17%) respectively. 172 patients (86%) had head trauma without structural injury, while only 28 patients (14%) had suffered from structural damage. 52 patients (26%) had severe TBI with loss of consciousness of at least 1 h or a PTA for at least 24 h after the accident, while 148 (74%) had not. 50 (25%) were admitted to the ICU and 150 (75%) to the ward. 38 patients (19%) had stayed in the hospital for more than a week and 162 (81%) less than a week.

In Table 2, we had analyzed the factors affecting the development of pituitary dysfunction after TBI. 122 patients had developed pituitary dysfunction after exposure to head trauma, while 78 had not. There was no significant difference between males and females in the development of pituitary dysfunction, 104 (85.2%) and 18 (14.8%), respectively.

Patients who were exposed to RTA were more likely to have pituitary issues, which impacted 81 (66.4%) of the patients. Pituitary dysfunction was found in 103 individuals (84.4%) with non-structural impairment. Pituitary injury was found in 19 of the individuals who had structural damage. Pituitary dysfunction was shown to be more prevalent in patients who had non-structural injury.

The location of hospitalisation was the second important influencing factor; 48 of 50 patients admitted to the ICU acquired a pituitary abnormality. The longer a patient is in the hospital, the more likely they are to acquire pituitary dysfunction in the future: out of 38 individuals, 37 had pituitary dysfunction after being hospitalised for more than a week.

Table 3 demonstrates that the GH was the most impacted hormone by head trauma in 100 patients (50%) followed by the gonadal axis, TSH, and lastly ACTH, 40 (20%), 21 (10.5%), and 10 (5%), respectively. Table 4 shows that the most common anomaly was a single hormonal deficit in 87 (43.5%) of the patients, followed by two axis defect in 9 (4.5%), and only three

patients (1.5%) had four Axis deficiencies, with no one diagnosed with three lines defect.

Table 1: Descriptive parameters of the study population

Descriptive parameters	Frequency (%)
Gender	
Male	175 (87.5)
Female	25 (12.5)
Age at onset of TBI (years)	
<18	48 (24)
18-44	130 (65)
>45	22 (11)
Time since TBI	
3 – 12 months	55 (27.5)
1-5 years	55 (27.5)
>5 years	90 (45)
Type of trauma	
RTA	142 (71)
Blast	24 (12)
Blunt	34 (17)
Type of injury	
Non structural	172 (86)
Structural	28 (14)
PTA	
Less than a day	148 (74)
More than a day	52 (26)
Site of hospitalization	
Ward	150 (75)
ICU	50 (25)
Duration of hospitalization	
Less than a week	162 (81)
More than a week	38 (19)

RTA: Road traffic accident, TBI: Traumatic brain injury, ICH: Intracranial hematoma, PTA: Post traumatic amnesia, ICU: Intensive care unit

Table 2: Assessment of frequency of pituitary dysfunction

Descriptive parameters	Yes (122)	No (78)	P value
Gender			
Male	104 (85.2)	71 (91)	0.876
Female	18 (14.8)	7 (9)	
Age at onset of TBI (years)			
<18	22 (18)	26 (33.3)	0.776
18-44	90 (73.8)	40 (51.3)	
>45	10 (8.2)	12 (15.4)	
Time since TBI			
3 – 12 months	14 (11.5)	41 (52.6)	0.800
1-5 years	40 (32.8)	15 (19.2)	
>5 years	68 (55.7)	22 (28.2)	
Type of trauma			
RTA	81 (66.4)	61 (78.2)	0.251
Blast	18 (14.7)	6 (7.7)	
Blunt	23 (18.9)	11 (14.1)	
Type of injury			
Non structural	103 (84.4)	69 (88.5)	0.277
Structural	19 (15.6)	9 (11.5)	
PTA			
Less than a day	121 (99.2)	27 (34.6)	<0.001*
More than a day	1 (0.8)	51 (65.4)	
Site of hospitalization			
Ward	74 (60.7)	76 (97.4)	0.007*
ICU	48 (39.3)	2 (2.6)	
Duration of hospitalization			
Less than a week	85 (69.7)	77 (98.7)	0.112
More than a week	37 (30.3)	1 (1.3)	

P value <0.05 is considered statistically significant

Table 3: Description of deficiency axis

Parameters	Frequency (%)
GH deficiency	100 (50)
LH, FSH deficiency	40 (20)
TSH deficiency	21 (10.5)
ACTH deficiency	10 (5)

GH: Growth hormone, LH: Leutinizing hormone, TSH: Thyroid stimulating hormone, FSH: Follicular stimulating hormone, ACTH: Adrenocorticotropic hormone

Table 4: Numbers of deficient axis

Numbers of deficiencies	Frequency (%)
1	87 (43.5)
2	9 (4.5)
3	0
4	3 (1.5)

Discussion

The greater number of males in comparison to females might be explained by the fact that males are more likely to be involved in an accident, especially in an oriental civilization. This might also be true for the reason that RTA is the most prevalent cause of TBI in our patients. Our patients had acquired pituitary dysfunction in about 61 percent of cases, which was slightly greater than the results of earlier research, which ranged from 15 percent to 56 percent. Schneider *et al*. discovered that at least 56 percent of their patients had some form of pituitary malfunction after a TBI in their research [9].

Biochemically, it is impossible to tell whether those anomalies existed before to the accident or thereafter; but, if they did, the patient must have observed them symptomatically prior to the injury [10]. In this study, statistical analysis failed to find a significant effect of gender on the likelihood of having pituitary problems after TBI, a common finding observed by most investigators such as Aimaretti *et al*., [11] Agha *et al*. [12] in their studies; however, this is in contrast to the findings of Popovic *et al*., [13] who found a positive relationship in males and Klose *et al*., [14] who found a positive relationship in females.

Some authors have mentioned the effect of time lapse after TBI on the presence of pituitary dysfunction, such as Bondanelli *et al*. [15] and Popovic *et al*. [13], who found that as time passes after the trauma, the likelihood of having some sort of pituitary impairment increases, which is the same finding we saw in our study. The formation of antipituitary antibodies as a result of TBI is one of the explanations for this discovery.

According to Agha *et al*. [12] and Schneider *et al*. [9], the discovery of a link between structural head traumas and the development of pituitary dysfunction was prevalent among investigators.

Looking for the aforementioned elements that alter pituitary function after trauma will add to the evidence that antipituitary antibodies are a key contributor to the development of chronic pituitary dysfunction that can last months. [16] When it comes to the length of hospitalisation and its impact on pituitary function, Klose [14] and Schneider *et al*. [9] discovered that the longer the hospital stay, the more pituitary dysfunction develops, which is the same conclusion we obtained in our study. Although it has not been investigated previously, our result of a higher incidence of pituitary dysfunction in ICU admissions compared to ward admissions may be simply explained by the fact that the more severe the TBI, the higher the frequency of pituitary dysfunction.

The majority of the researchers discovered that GH insufficiency is the most common pituitary endocrine abnormality following

TBI. Klose *et al*., [14] found the same outcome as we did in our research. This can be explained by the fact that the somatotrophs, which are acidophilic cells, are located in the lateral aspect of the adenohypophysis, the pars lateralis, putting it in close contact with the bony walls of the gland and thus making it more vulnerable to trauma; additionally, GH secreting cells receive their blood supply from the long portal vessels that run in the peripheral aspect of the pituitary gland, putting it in a position where it is more vulnerable According to some researchers, the gonadal axis defect is the most common [9, 17, 18]. We and other authors, such as Lieberman *et al*. [19], discovered that single hormonal defects were considerably more prevalent than combined hormonal shortages, with 51 percent vs 17 percent for single versus combination deficits.

Conclusion

We determined that chronic post-TBI pituitary dysfunction is more common than expected in the group investigated, with a single hormonal deficiency being the most common aberration, with the GH axis being the most impacted and the ACTH being the least affected.

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