

# Patterns of pituitary dysfunction three months or more after traumatic brain injury

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## ABSTRACT

**Purpose:** Chronic posttraumatic brain injury (TBI) pituitary dysfunction is not a newly discovered subject, it has been reported more frequently, probably due to increasing chances of exposure to its causes, mainly the road traffic accidents, sport-related injuries, falls, and injuries during wars. This study aims to estimate the frequency of pituitary dysfunction 3 months or more after head trauma and the patterns of hormonal deficiencies. **Methods:** A cross-sectional study was conducted between January 2016 and August 2017. 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. Statistical Package for the Social Sciences (SPSS) version 23.0 was used for univariate analysis,  $P < 0.05$  was considered statistically significant. **Results:** Out of the 28 patients involved in this study, 17 (61%) had pituitary dysfunction, while 11 (39%) had not. Single hormonal defect was the most prevalent abnormality in 12 (43%), and the most affected hormone was the growth hormone (GH) in 14 patients (50%), followed by gonadal axis, thyroid stimulating hormone, and finally adrenocorticotrophic hormone (ACTH), 6 (21%), 3 (11%), and 1 (4%), respectively. **Conclusion:** TBI pituitary dysfunction is more prevalent than was predicted in the population studied, single hormonal defect was found to be the most prevalent abnormality, being the GH is the most affected axis, and the ACTH seems to be the least.

**Key words:** Growth hormone deficiency, head trauma, hypopituitarism, traumatic brain injury

## INTRODUCTION

Posttraumatic brain injury (TBI) pituitary dysfunction is not a newly recognized subject, especially chronic pituitary dysfunction which has been reported with an increasing frequency, notably, due to increasing chance of exposure to its leading causes, mainly road traffic accidents (RTA) and wars.<sup>[1]</sup>

TBI is defined as “an alteration in brain function, or other evidence of brain pathology, caused by an external force.”<sup>[2]</sup>

The acute phase of TBI represents the first 2 weeks after the trauma, while the chronic phase starts 3 months later.<sup>[3]</sup>

Most of the cases are attributed to RTA, while other major causes are those related to a variety of sport acts, mainly boxing and kickboxing. War-related head injuries also contribute to a large aspect of TBI, especially in countries suffered from recent conflicts.<sup>[4]</sup>

The vascular theory,<sup>[5]</sup> direct trauma,<sup>[6]</sup> and the development of antipituitary antibodies<sup>[7]</sup> are the main theories explaining post-TBI hypopituitarism.

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This study aimed at estimating the frequency and analyzing the patterns of pituitary dysfunction in the chronic phase of TBI.

## SUBJECTS AND METHODS

This was a cross-sectional study conducted between January 2016 and August 2017. Participants were patients having a history of previous exposure to TBI.

TBI can be classified, from severity point of view, into mild, moderate, and severe according to the severity of the functional neurological deficit and the associated structural brain injuries. Chronologically, it could be either acute or chronic, the former represents the first 2 weeks after the onset of TBI, while the chronic phase starts after the 3<sup>rd</sup> month from the onset.<sup>[3]</sup>

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.<sup>[8]</sup>

### Inclusion criteria

Patients having a history of exposure to head trauma for at least 3 months before enrolment and 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.

### Variable tested

After informed verbal consent was taken from the patients or their next of kin, anthropometric and clinical data have been taken from each patient in the form of:

- Age
- Gender
- Duration of hospitalization
  - Less than a week
  - More than a week
- Site of hospitalization
  - Ward
  - Intensive Care Unit (ICU)
- PTA (for assessment of severity of TBI)
  - Mild TBI: PTA <1 h

- Moderate TBI: PTA <24 h
- Severe TBI: PTA >24 h
- Type of trauma
  - Blast
  - Blunt
  - RTA
- Type of TBI
  - Nonstructural
  - Structural
    - Skull fractures
    - Intracerebral hemorrhage (ICH).

Any patient who had no pituitary imaging after the trauma was sent for pituitary directed neuroimaging, in particular to exclude any structural pituitary abnormalities.

### Biochemical testing

A detailed history and physical examination was done for all patients, looking for any signs and symptoms of endocrine disorder, then patients were given appointment to do pituitary function test on another day to do the baseline and the dynamic tests.

For each person, 10 ml of blood were taken during the work time 8:30 am in fasting state. All samples were collected in tubes containing clot activator, except plasma adrenocorticotrophic hormone (ACTH) samples were collected in ethylenediaminetetraacetic acid tube.

All samples, except insulin-like growth factor-1 (IGF-1) which was examined by ELISA (DRG), were examined in fully automated chemiluminescence immunoassay kits Cobas e411 analyzer series Roche diagnostics.

Early morning blood samples were obtained for 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 (FT4).

For assessment of growth hormone (GH), baseline IGF-1 and GH were measured, then glucagon is administered intramuscularly at a dose of 1 mg; GH then measured at 2 and 3 h. GH deficiency is diagnosed if peak GH level is less than 7.1 ng/mL. IGF1 value less than the normal reference for age is regarded as abnormal.<sup>[9]</sup>

Baseline ACTH and cortisol were measured followed by ACTH stimulation test, in which 250 µg of cosyntropin (alpha 1–24 corticotrophin) was administered intramuscularly and cortisol levels were determined immediately before and again after 30 and 60 min, in which peak cortisol level of

<20 µg/dL is regarded as deficient, and finding of normal or low ACTH (normal value = 10–60 pg/mL) indicate a pituitary–adrenal axis dysfunction.<sup>[10]</sup>

Central hypothyroidism diagnosis was considered by the finding of low fT4 (normal value = 0.93–1.7 ng/dL) or low TT4 (normal value = 5.1–14.1 µg/dL) concentrations associated with low/normal TSH levels (normal value = 0.27–4.2 µIU/ml).<sup>[11]</sup>

Hypogonadotropic hypogonadism (HH) in males was diagnosed by low or low-normal FSH level and low or low-normal LH level together with low testosterone level,<sup>[12]</sup> with cutoff value of testosterone 300 ng/dL [10–40 nmol/L], and for FSH (1–13 mIU/mL) and for LH (1–9 mIU/mL). While in females, low morning estradiol levels (normal values = 15–300 pg/mL) in the setting of normal or low gonadotropins are diagnostic of HH (FSH = 2–12 mIU/mL [follicular], 20–80 mIU/mL [midcycle], and 0.5–18 mIU/mL [luteal]).

## RESULTS

The vast majority of the patients who have been excluded from the study were because they had mild TBI. Some other patients had not completed their investigations for a reason or another, while others had some reluctance to participate. The remainder were only 28 patients who have been involved.

Table 1 shows the general characteristics of the patients involved in this study: from those 28 patients, 20 (71%) were male and 8 (29%) were female. The age distribution at the time of the study was as follows: patients aged <18 years old were 6 (21%), 18–44 years old were 18 (64%), and those aged >44 years were 4 (14%) with a mean age of 29.6 ± 2.7 years, while the distribution at the onset of the accidents was 12 (43%), 14 (50%), 2 (7%) for age groups <18, 18–44, and 45 years old and above, respectively, with the mean age 22.5 ± 2.5 years.

RTA was responsible for TBI in 20 patients (71%), while blast and blunt injuries were the causes in 4 (14%) for each. Twenty-five patients (89%) had head trauma without structural injury, while only three patients (11%) had suffered from structural damage, from them, 2 (7%) had skull fracture and 1 (4%) had ICH.

Eight patients (29%) had severe TBI with loss of consciousness of at least 1 h or a PTA for at least 24 h after the accident, while 20 (71%) had not. Eight (29%) were admitted to the ICU and 20 (71%) to the ward.

**Table 1: General description of the patients**

	Frequency (%)
Gender	
Male	20 (71.4)
Female	8 (28.6)
Age at enrolment	
<18	6 (21.4)
18-44	18 (64.3)
45 and more	4 (14.3)
Age at onset of TBI	
<18	12 (42.9)
18-44	14 (50)
45 and more	2 (7.1)
Time since TBI	
3-12 months	8 (28.6)
1-5 years	8 (28.6)
5 years and more	12 (42.9)
Type of trauma	
RTA	20 (71.4)
Blast	4 (14.3)
Blunt	4 (14.3)
Type of injury	
Nonstructural	25 (89.3)
Structural	3 (10.7)
Type of structural injury	
Non	25 (89.3)
Skull fracture	2 (7.1)
ICH	1 (3.6)
PTA	
Less than a day	20 (71.4)
More than a day	8 (28.6)
Site of hospitalization	
Ward	20 (71.4)
ICU	8 (28.6)
Duration of hospitalization	
Less than a week	24 (85.7)
More than a week	4 (14.3)

TBI: Traumatic brain injury, RTA: Road traffic accident, ICH: Intracranial hematoma, PTA: Posttraumatic amnesia, ICU: Intensive Care Unit

Four patients (14%) had stayed in the hospital for more than a week and 24 (86%) less than a week. There were eight patients (29%) investigated within the 1<sup>st</sup> year after the accident, another eight (29%) after 1 year, and 12 (43%) after the 5<sup>th</sup> year with mean time of 86 ± 21 months (7 ± 1.8 years).

In Table 2, we had analyzed the factors affecting the development of pituitary dysfunction after TBI.

Seventeen patients (61%) had developed pituitary dysfunction after exposure to head trauma, while 11 (39%) had not [Figure 1]. There was no significant difference between males and females in the development of pituitary dysfunction, 12 (60%) and 5 (62%), respectively [Figure 2].

Interestingly, the more the duration after the onset of TBI, the more the likelihood to have a pituitary dysfunction, 3 (38%), 5 (63%), and 9 (75%), respectively, for the groups of less than a year, 1 year to 5 years, and those with >5 years past the trauma, with mean duration of 94 ± 25.5 months

(7 ± 2 years) for patients with pituitary dysfunction versus 75 ± 36.3 months (6 ± 3 years) for the others [Figure 3].

Patients exposed to RTA and blast injuries were more prone to have pituitary problems, 13 (65%) and 3 (75%), respectively, in comparison to blunt trauma 1 (25%).

All the three patients who had suffered from structural head injuries and they developed pituitary dysfunction, while exposure to a TBI without structural injuries had modest effect: 14 (56%) affected versus 11 (44%) had normal pituitary function.

The most affected factor in the development of pituitary dysfunction was the conscious level at time of trauma, none of the patient who had not lost their consciousness for more than an hour at the onset of the accident nor lost their memory for more than a day, had developed pituitary defect, while the 17 patients (85%) who had lost their consciousness or memory had developed some sort of pituitary dysfunction.

The second significant affected factor was the site of hospitalization, all the eight patients who had been admitted to the ICU they developed pituitary defect, while patients admitted to the ward showed equivocal results: nine patients (45%) versus 11 (55%) for pituitary dysfunction and normal function, respectively.

The more the duration of hospitalization, the more the likelihood of having some sort of pituitary dysfunction in the future: all the four patients who had been admitted more than a week developed some sort of pituitary dysfunction, while only 13 patients (54%) who were admitted less than a week developed pituitary dysfunction and 11 (45%) had not.

Table 3 shows that the most affected hormone by head trauma was the GH in 14 patients (50%), followed by the gonadal axis, TSH, and finally ACTH, 6 (21%), 3 (11%), and 1 (4%), respectively [Figure 4].

In Table 4, we can see that a single hormonal defect was the most prevalent abnormality in 12 (43%), followed by two-axis defect in 2 (14%) and only one patient (4%) had suffered from four axes deficiencies, while there has been no one diagnosed with three lines defect [Figure 5].

Further analysis of these findings can be shown in Table 5. all the five females who developed pituitary dysfunction had only one line defect, while 7 males (58%) had one defect, 4 (33%), and 1 (8.3%) had two and four defects, respectively.

**Table 2: Frequency of pituitary dysfunction**

	Yes, n (%)	No, n (%)	P
Total	17 (60.7)	11 (39.3)	
Gender			
Male	12 (60)	8 (40)	0.903
Female	5 (62.5)	3 (37.5)	
Age at enrolment			
<18	3 (50)	3 (50)	0.729
18-44	11 (61.1)	7 (38.9)	
45 and more	3 (75)	1 (25)	
Age at onset of TBI			
<18	7 (58.3)	5 (41.7)	0.905
18-44	9 (64.3)	5 (35.7)	
45 and more	1 (50)	1 (50)	
Time since TBI			
3-12 months	3 (37.5)	5 (62.5)	0.241
1-5 years	5 (62.5)	3 (37.5)	
5 years and more	9 (75)	3 (25)	
Type of trauma			
RTA	13 (65)	7 (35)	0.268
Blast	3 (75)	1 (25)	
Blunt	1 (25)	3 (75)	
Type of injury			
Nonstructural	14 (56)	11 (44)	0.140
Structural	3 (100)	0	
Type of structural injury			
Non	14 (56)	11 (44)	0.337
Skull fracture	2 (100)	0	
ICH	1 (100)	0	
PTA			
Less than a day	17 (85)	3 (15)	0.000
More than a day	0	8 (100)	
Site of hospitalization			
Ward	9 (45)	11 (55)	0.008
ICU	8 (100)	0	
Duration of hospitalization			
Less than a week	13 (54.2)	11 (45.8)	0.116
More than a week	4 (100)	0	

TBI: Traumatic brain injury, RTA: Road traffic accident, ICH: Intracranial hematoma, PTA: Posttraumatic amnesia, ICU: Intensive Care Unit

**Table 3: Frequency of each axis deficiency**

	Frequency (%)
GH deficiency	14 (50)
LH, FSH deficiency	6 (21)
TSH deficiency	3 (11)
ACTH deficiency	1 (4)

GH: Growth hormone, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, TSH: Thyroid-stimulating hormone, ACTH: Adrenocorticotropic hormone

On the other side, exposure to TBI at early onset in life will give more chance to developed more hormonal deficiencies. In addition, patients who had exposed to TBI for >5 years are more prone to have multiple defects, mean age for four hormonal defect was 21 years, two defects 26 ± 4.8 years, and 23 ± 4 years for the single defect.

A significant finding in our study is that blast and blunt trauma were always associated with more than one defect, for the blast injuries: Two (67%) had two defects and one (33%) has four defects, while for blunt trauma, only one

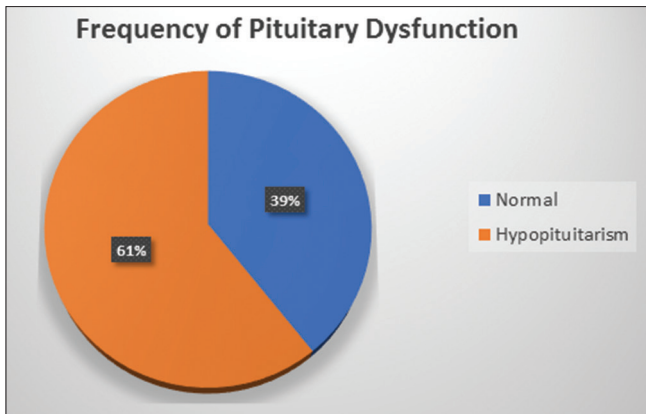


Figure 1: Frequency of pituitary dysfunction after traumatic brain injury

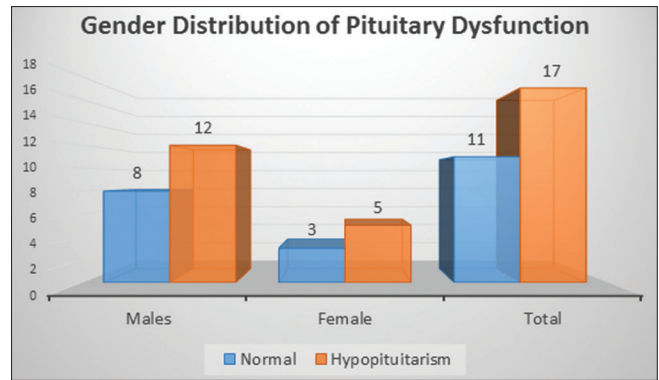


Figure 2: Gender distribution of pituitary dysfunction after traumatic brain injury

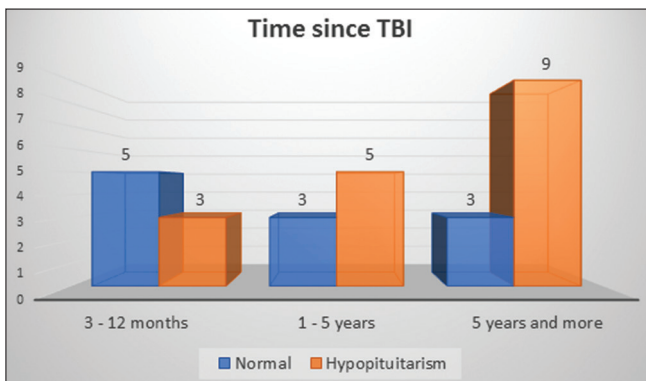


Figure 3: Frequency of pituitary dysfunction with time since traumatic brain injury

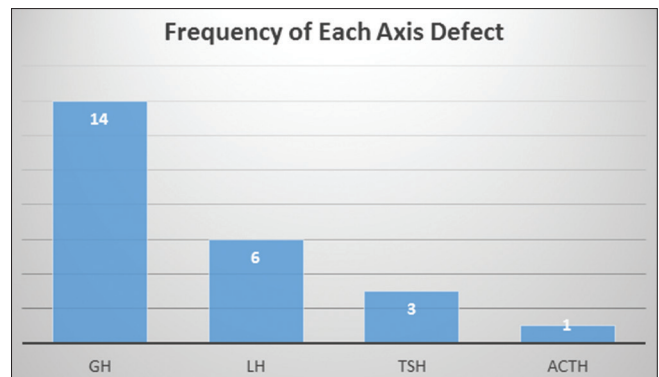


Figure 4: Frequency of each axis deficiency after traumatic brain injury

patient had two defects. In contrast to RTA where most of the patient, 12 (92%) had only one defect and 1 patient had two defects. This finding was also noticed in a significant manner with patients suffered from TBI that was associated with structural head injury: none with single-axis defect, 2 (66%) with two lines, and 1 (33%) with four lines defect, while traumas without structural injuries were mostly accompanied by single hormone defect in 12 (86%) and 2 (14%) for two axes defects.

Patients who had not been admitted to the ICU were more likely to have one hormone defect in comparison with patients admitted to the ICU, for patients with no ICU admission: Eight (89%) with single defect and 1 (11%) with two defects and none with more than two defects, while for ICU patients: 4 (50%), 3 (38%), and 2 (13%) for one, two, and four defects, respectively.

This was also true in a statistically significant manner for patients admitted for less than a week in comparison with those admitted for more than a week, where 11 patients (85%) who had stayed in the hospital for less than a week, developed single-line defect and 2 (15%) developed two lines defect, whereas 1 patient (25%), 2 (50%), and 1 (25%) had developed

one, two, and four lines defect, respectively, when the period of admission was more than a week.

Notably, type of structural injury has no effect in determining the number of axes defect.

## DISCUSSION

The high proportion of males in relation to females could be attributed to that the opportunity for exposure to an accident would be naturally more in males, especially in an oriental society. This also can be true for the explanation for being the RTA is the most common cause of TBI in our patients.

About 60% of our patients had developed some sort of pituitary dysfunction; this observation was a little bit higher than the results of similar studies that were ranging from 15% to 56%.

Schneider *et al.* have found in their study that at least 56% of their patients would have some degree of pituitary dysfunction following TBI,<sup>[13]</sup> while the results obtained from Leal-Cerro *et al.* was 24.7%.<sup>[14]</sup>

Some studies found a percentage as low as 5.4% as Kokshoorn *et al.* had found in their study.<sup>[15]</sup>

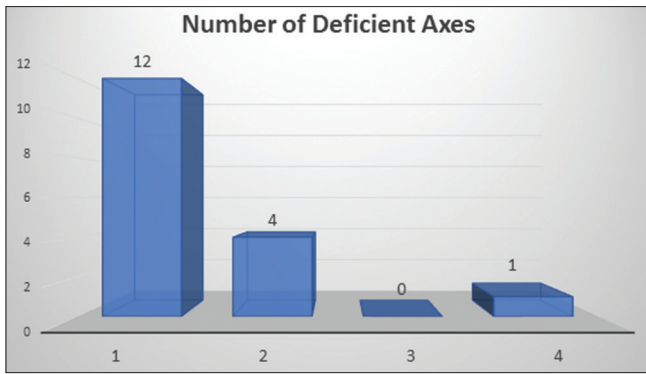


Figure 5: Number of hormonal deficiencies after traumatic brain injury

Whether those patients were having those abnormalities before the accident or later on cannot be differentiated biochemically, however, if so, it must be symptomatically noticed by the patient before the insult.<sup>[16]</sup>

In this study, statistical analysis failed to find a significant effect of gender on the possibility of having pituitary problems following TBI, a common finding that was also observed by most investigators like Aimaretti *et al.*, Agha *et al.*, and Tanriverdi *et al.* in their studies,<sup>[17-19]</sup> however, this is in contrast to the finding of Popovic *et al.*, who found a positive relation in males<sup>[20]</sup> and Klose *et al.*, who found a positive relation to females.<sup>[21]</sup>

Although we did not find a positive relationship between pituitary dysfunction and the age at which the accident had happened, as some authors have notices like Agha *et al.*, Bondanelli *et al.*, and Schneider *et al.*, who found a positive relationship with older age.<sup>[18,22,23]</sup>

However, some authors had found some kind of gender-wise relationships, as Sara Preiss when she found a positive association in older females only.<sup>[24]</sup> Moreover, Popovic who found a positive relation with older males,<sup>[20]</sup> while Schneider *et al.* found a positive relationship only to GH in older patients.<sup>[13]</sup>

Some authors had mentioned the effect of time lapse after TBI and the presence of pituitary dysfunction, as Bondanelli *et al.*<sup>[22]</sup> and Popovic, who had found an increased possibility of having some sort of pituitary impairment as more time has passed after the trauma,<sup>[20]</sup> the same finding we have seen in our study, while Schneider *et al.*<sup>[25]</sup> and Ghigo *et al.*<sup>[26]</sup> had not found a significant association.

One of the explanations for this finding is the development of antipituitary antibodies as a consequence of exposure to TBI.<sup>[7]</sup>

Number of deficiencies	Frequency (%)
1	12(42.9)
2	4(14.3)
3	0(0.0)
4	1(3.6)

	Number of deficient axes			P
	1, n (%)	2, n (%)	4, n (%)	
Total	12 (70.6)	4 (23.5)	1 (8.3)	
Gender				
Male	7 (58.3)	4 (33.3)	1 (8.3)	0.229
Female	5 (100)	0	0	
Age at enrolment				
<18	3 (100)	0	0	0.756
18-44	7 (63.6)	3 (27.3)	1 (9.1)	
45 and more	2 (66.7)	1 (33.3)	0	
Age at onset of TBI				
<18	5 (71.4)	1 (14.3)	1 (14.3)	0.657
18-44	5 (66.7)	3 (33.3)	0	
45 and more	1 (100)	0	0	
Time since TBI				
3-12 months	2 (66.7)	1 (33.3)	0	0.889
1-5 years	4 (80)	1 (20)	0	
5 years and more	6 (66.7)	2 (22.2)	1 (11.1)	
Type of trauma				
RTA	12 (92.3)	1 (7.7)	0	0.006
Blast	0	2 (66.7)	1 (33.3)	
Blunt	0	1 (100)	0	
Type of injury				
Nonstructural	12 (85.7)	2 (14.3)	0	0.006
Structural	0	2 (66.7)	1 (33.3)	
Type of structural injury				
Non	12 (85.7)	2 (14.3)	0	0.386
Skull fracture	0	1 (50)	1 (50)	
ICH	0	1 (100)	0	
PTA				
Less than a day	NA (NA)	NA (NA)	NA (NA)	NA
More than a day	NA (NA)	NA (NA)	NA (NA)	
Site of hospitalization				
Ward	8 (88.9)	1 (11.1)	0	0.193
ICU	4 (50)	3 (37.5)	1 (12.5)	
Duration of hospitalization				
Less than a week	11 (84.6)	2 (15.4)	0	0.042
More than a week	1 (25)	2 (50)	1 (25)	

TBI: Traumatic brain injury, RTA: Road traffic accident, ICH: Intracranial hematoma, PTA: Posttraumatic amnesia, ICU: Intensive Care Unit, NA: Not available

As we have found that blast injuries were associated with more prevalence of pituitary dysfunction, as Baxte *et al.* had found that blast injuries were responsible for >60% of pituitary dysfunction versus <3% for nonblast injuries.<sup>[27]</sup>

The finding of the association between structural head injuries and the development of pituitary dysfunction was common among investigators, as seen by Agha *et al.*, Schneider *et al.*, and Kelly *et al.*,<sup>[18,23,28]</sup> apart from Bondanelli *et al.*, who did not find such significant relationship.<sup>[22]</sup>

Yang *et al.* found that basal skull fracture was more significantly associated with pituitary dysfunction than ICH.<sup>[29]</sup>

The association between the conscious level following the trauma and the pituitary dysfunction has been extensively investigated, with some found a positive relationship,<sup>[21,22,28]</sup> while others could not find such a relationship.<sup>[13,17,19,20,30]</sup>

Looking for the above factors affecting the pituitary function after trauma will give more support to the theory of antipituitary antibodies as a major contributing factor for the development of chronic pituitary dysfunction that could persist for months.<sup>[31]</sup>

Regarding the duration of hospitalization and its effect on the pituitary function, Klose and Schneider *et al.* found that the longer the duration of hospital stay, the more the pituitary dysfunction to develop,<sup>[21,32]</sup> the same finding we share with them in our study.

Our finding of increased prevalence of pituitary dysfunction in ICU admission in comparison to the admission to the ward, although it has not been studied by a previous authors, can be easily explained by the fact that the more the severe TBI, the more the need for ICU stay.

Most of the investigators had found that GH deficiency is the most prevalent pituitary endocrine defect after TBI, as Tanriverdi *et al.*, 44%;<sup>[31]</sup> Aimaretti *et al.*, 18.6%;<sup>[17]</sup> Klose *et al.*, 15%;<sup>[21]</sup> and Popovic *et al.*, 15%;<sup>[20]</sup> the same result we have obtained from our study. This can be explained by the fact that the somatotrophs which are acidophilic cells are situated in the lateral aspect of the adenohypophysis, the pars lateralis, make it close contact to the bony walls of the gland and thus more vulnerable for trauma, besides, GH-secreting cells blood supply is from the long portal vessels which run in the peripheral aspect of the pituitary gland, this position put it in the hazard of being easily vulnerable to trauma.

Other authors have found the gonadal axis defect to be the most prevalent like Wachter *et al.*, 12.7% versus 1.8% for GHD; Herrmann *et al.*, 17% versus 8%;<sup>[33]</sup> Schneider *et al.*, 20% versus 10%;<sup>[13]</sup> and Leal-Cerro *et al.*, 17% versus 5.8%.<sup>[14]</sup>

Only Agha *et al.* have found ACTH deficiency to be the most prevalent axis defect in his study 12.7% versus 10.7% for GHD and 11.8% for gonadal axis defect,<sup>[18]</sup> while TSH deficiency was most prevalent in the study of Berg *et al.*, 12% versus 5% for GHD.<sup>[34]</sup>

Single hormonal defect was far more common than combined hormonal deficiencies, a common observation found by us and other authors like Lieberman *et al.*, where he found 51% versus 17% for single versus combined deficiencies;<sup>[30]</sup> Kopczak *et al.* who found 28.5% versus 4.5%;<sup>[35]</sup> and Tanriverdi *et al.* 41% versus 10%, respectively,<sup>[19]</sup> which are in concordance with our findings.

## CONCLUSION

We have discovered that chronic post TBI pituitary dysfunction is more prevalent than predicted in the population studied, single hormonal defect was found to be the most prevalent abnormality, being the GH is the mostly affected axis and the least hormone to be affected was the ACTH.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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