Pituitary Hormonal Imbalance after Moderate to Severe Traumatic Brain Injury Patients: Analytical Prospective Study

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Abstract

Background: Traumatic brain injury (TBI) is a major cause of death and disability worldwide. In Egypt moderate and severe TBI represents 17.2% of presenting cases. The frequency of hypopituitarism after TBI varies widely among different studies (15-50% of the patients with TBI in most studies).

Aim of Study: The aim of this study is to estimate the prevalence of pituitary hormonal imbalance in moderate to severe Traumatic Brain Injury (TBI) patients in Egypt.

Patients and Methods: Analytical prospective study with sample size of 23 patients admitted in Cairo University Hospitals from December 2020 to April 2021 with our inclusion criteria.

Hormonal Assay level was used to detect Hormonal deficiency.

Serum ACTH, Morning Cortisol, TSH, LH, FSH, and GH were measured within 24 hrs. from time of trauma and follow-up after 2 weeks, 1 month and 2 months and stratified according to matching Age and sex.

Results: Out of the 23 included in the study 6 patients (26%) were found to have pituitary hormonal imbalance; 2 patients (8.7%) have GH deficiency, 2 patients (8.7%) with ACTH/cortisol deficiency, one patient (4.35%) with LH deficiency and one patient (4.35 %) with TSH deficiency and one of affected patients with increased urine output (CDI).

Overall age ranged from 2 years to 40 years with a mean age 12.1 years ± 7.74 Years. 15 patients (65.2%) were males and 8 patients (34.8%) were females.

Out from 6 patients that have NED, 4 patients (66.7%) had severe head, 2 patients (33.3%) had moderate head injury. Out of 6 patients that have NED 2 patients (33.3%) underwent conservative treatment and 4 patients (66.6%) underwent neurosurgical intervention.

Conclusion: Pituitary hormonal imbalance is one of the long term sequelae of traumatic Brain injury. Many patients are under-diagnosed because symptoms of mild hypopituitarism are slowly developing. Growth Hormone and ACTH are the most frequent pituitary hormone deficiencies in patients who have sustained TBI. It should not be underestimated because hormonal abnormalities may contribute to a diminished quality of life.

Key Words: Pituitary hormonal imbalance – Traumatic brain injury – Post-traumatic hypopituitarism.

Introduction

TRAUMATIC brain injury (TBI) is a growing public health problem worldwide and is a leading cause of death and disability [1].

Updated statistical records for TBI in Egypt are unavailable, however TBI represents a serious public health problem in Egypt with moderate and severe TBI representing 17.2% of presenting cases [2]. Traumatic brain injury can manifest clinically from concussion to coma to death. They can be classified according to severity based on Glasgow coma scale into mild (GCS: 13-15), moderate (GCS: 9-12) and severe (GCS: 3-8) [3]. In 2007, Schneider et al., reported a systematic review about neuroendocrine dysfunction following subarachnoid hemorrhage and traumatic brain injury between 2000 and 2007 including 19 studies and 1137 patients [3]. They reported the pooled prevalence of hypopituitarism in the chronic phase after traumatic brain injury and aneurysmal subarachnoid hemorrhage was (27.5%). Based on data in the current literature, approximately 15%-20% of TBI patients develop chronic hypopituitarism, which clearly suggests that TBI-induced hypopituitarism is more frequent in contrast with previous assumptions [1].

Aim of work:

To evaluate the prevalence of Pituitary Dysfunction in Post Traumatic Brain Injury patients and Treatment of hormonal deficiency in coopera-
tion with Endocrinologists aiming at improving patient's quality of life.

**Patients and Methods**

We made analytical prospective study with sample size of 23 patients, which was designed to estimate the prevalence of pituitary hormonal imbalance in moderate to severe traumatic Brain Injury patients who had been admitted to Emergency Department in Cairo University Hospitals from December 2020 to April 2021. Twenty three Patients who experienced moderate or severe TBI needing hospital admission in Cairo University (Kasr Al-Ainy) Hospitals with our inclusion criteria from December 2020 to April 2021 were included in this study. Screening for Neuro endocrine Dysfunction was done using Hormonal assay.

SPSS software (statistical package for the social sciences, version 24, SPSS Inc, Chicago IL, USA) was used to calculate the sample size of this analytical prospective study. Assuming 80% power, 0.05 level of significance, 20% null hypothesis value and estimated proportion of 10%. The sample size used is 23 patients. We included Twenty three patients in acute phase of TBI (from day one after TBI) with history of admission at Neurosurgery Department, Accidents & Emergency Unit at Kasr Al-Ainy. They will be screened for hormonal affection. The age group (2-40) yr without co morbidities with moderate to severe of TBI who need hospitalization for at least 48 hours and who need ICU monitoring, in particular, should be screened during the acute phase and prospectively. For those with a history of complicated moderate TBI, or severe TBI to be followed-up for 2 months.

We excluded Mild TBI patients who are discharged from emergency units and/or who have no loss of consciousness and/or post-traumatic amnesia of less than 30 minutes. Also, TBI patients in a chronic stages, out of age group (2-40) years and patients with co morbidities were excluded.

**Présentation**: At follow-up after 2 months from trauma.

<table>
<thead>
<tr>
<th>Hormone deficiency</th>
<th>History</th>
<th>Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>Lethargy, weakness, myalgia, nausea, anorexia, weight loss</td>
<td>Pallor, hypotension</td>
</tr>
<tr>
<td>Gonadotrophins</td>
<td>Decreased libido, dyspareunia, amenorrhoea</td>
<td>Fine wrinkles, breastatrophy, paucity of body hair</td>
</tr>
<tr>
<td>TSH</td>
<td>Weight gain, cold intolerance, constipation, fatigue, low mood</td>
<td>Dry skin, slow relaxing reflexes, bradycardia</td>
</tr>
<tr>
<td>GH</td>
<td>Impaired concentration, memory and cognitive function, reduced exercise tolerance</td>
<td>Central adiposity, reduced lean mass</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Polyuria and polydipsia especially nocturnal</td>
<td></td>
</tr>
</tbody>
</table>

**Interpretation:**

Patients were recruited from the A&E Unit, Neurosurgery Department, Cairo University Hospitals.

Patients who had Head trauma that occurred within 24 hrs prior to admission followed emergency department in order to be recruited in the study.

Patient admitted to this study had moderate or severe head injury at time of trauma, only patients with inclusion criteria were included in the study. The date of head injury and the Glasgow Coma Scale (GCS) score at the time of presentation with injury were recruited from neurosurgery emergency sheet of the patients. History suggestive of fracture base e.g. bleeding per ear or nose and CSF per ear or nose, loss of Consciousness, vomiting, focal neurological signs and if whether conservative treatment or surgical intervention was done e.g. elevation of depressed fracture or evacuation of hematoma all were documented.

Images of the patient's i.e. CT brain and X-ray cervical spine were also revised at time of admis-sion.

**Severity of injury is indicated by the total score:**
- 3-8 = Severe, 9-12 = Moderate.

Twenty-three patients were recruited. Informed consent was obtained from the subjects.

Patients underwent series of endocrine tests to detect pituitary dysfunction if present. The following hormones were measured within 24 hours from trauma, after 2 weeks, 1 month and 2 months.
in all patients: ACTH, Morning cortisol, FSH, LH, TSH, GH. The Routine labs i.e. CBC, Coagulation profile, liver function tests and Kidney function tests were revised from the patient's files to check for their levels.

Results

This study included 23 patients admitted to Cairo university hospitals in the period between December 2020 to April 2021 with our inclusion criteria 6 patients (26%) out of the 23 were found to have Neuroendocrine Dysfunction.

Out of 23 patients included in the study 15 patients were males and 8 patients were females. Out of 15 male patients 4 patients (26.7%) had pituitary dysfunction and out of 8 female patients 2 patients (25%) had pituitary dysfunction.

Table (2): Distribution of the studied cases according to gender (n=23).

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number</th>
<th>Percent</th>
<th>Pituitary Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>15</td>
<td>65.2%</td>
<td>4 patients (26.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>34.8%</td>
<td>2 patients (25%)</td>
</tr>
</tbody>
</table>

Fig. (1): Distribution of cases according to gender.

Table (3): Distribution of studied patients according to age.

<table>
<thead>
<tr>
<th>Age</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>12.1 yrs</td>
</tr>
<tr>
<td></td>
<td>7.74</td>
</tr>
</tbody>
</table>

Table (4): Distribution of studied patients according to severity of trauma.

<table>
<thead>
<tr>
<th>Traumatic brain injury</th>
<th>Patients affected</th>
<th>Patients Not Affected</th>
<th>Total number of patients in study</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>4 (33.3%)</td>
<td>8</td>
<td>12</td>
<td>0.556733</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (18.2%)</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

Fig. (2): Percent of patients affected according to severity of Trauma.

Out from patients diagnosed with pituitary dysfunction, 4 patients (17.4%) had severe head injury i.e GCS 3-8/15 and 2 patients (8.7%) had moderate head injury i.e GCS 9-13/15.

Overall age ranged from 2 years to 40 years with a mean age 12.1 years ± 7.74 Years, while the mean age in affected group of patients is 11.6 years ± 9.4 years.

Out of 23 patients, 7 patients (30.4%) were injured following Fall from Height and 2 of them developed pituitary Dysfunction, 13 patients (56.5%) with history of Road Traffic accidents and 3 of them developed pituitary Dysfunction and 3 patients (13%) with Isolated Head Trauma and 1 of them developed pituitarydysfunction.

Table (5): Distribution of studied patients according to Mode of trauma.

<table>
<thead>
<tr>
<th>Mode of Trauma</th>
<th>Patients Affected</th>
<th>Patients Not Affected</th>
<th>Total Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall from height</td>
<td>2 (28.6%)</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Road Traffic Accident</td>
<td>3 (23%)</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Isolated Head Trauma</td>
<td>1 (33.3%)</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Fig. (3): Percent of patients affected according to Mode of Trauma.
Out of 6 patients that had Pituitary Dysfunction 2 patients from 23 (33.3%) underwent conservative treatment one of them the CT showed No Abnormality Detected (NAD) with manifestations of skull base fractures (raccooneye, CSF otorrhea) and the other one showed brain edema and the rest 6 of patients (66.7%) had Frontal and/or Temporal EDH that was surgically evacuated.

It is obvious in our study that the patients affected who had positive finding in the CT brain is in 100% of them in the Fronto-temporal region i.e. The trauma near pituitary hypothalamic region and no single case detected with trauma to occipital region or finding in the posterior fossa.

Out of 23 patients included in the study 6 patients (26%) diagnosed with pituitary dysfunction 2 patients had decrease in GH, 2 patients had decrease in ACTH and morning cortisol, 1 patient had decrease in LH and 1 patient had decrease in TSH and one of them had central diabetes insipidus and all of patient’s FSH level were within normal level whether male or female and pre/post puberty.

**Fig. (4): Percent of patients affected according to CT brain and clinical situation.**

**Fig. (5): Percent of Patients affected according to Hormonal deficiency.**

**Discussion**

Traumatic brain injury (TBI) is defined as damage to the brain resulting from external mechanical force, such as rapid acceleration or deceleration, impact, blast waves, or penetration by a projectile. Brain function is temporarily or permanently impaired and structural damage may or may not be detectable with current technology [4].

TBI represents a serious public health problem in Egypt with moderate and severe TBI representing 17.2% of presenting cases [2].

Traumatic brain injury can manifest clinically from concussion to coma to death. They can be classified according to severity based on Glasgow coma scale into mild (GCS: 13-15), moderate (GCS: 9-12) and severe (GCS: 3-8) [5].

Patients suffering TBI are typically brought to a hospital emergency room for initial diagnosis and treatment. Once vital signs are assessed and stabilized, and other life-threatening injuries are identified and treated, the process of diagnosing the extent of brain injury begins [4].

Traumatic brain injury is a clinical diagnosis, relying on history of trauma followed by symptoms such as: Headache, nausea, confusion, personality change, and documented loss of consciousness, amnesia (anterograde or retrograde), speech difficulties, and other changes in mental status, impaired vision or double vision, and weakness [6].

CT is routinely used to assess all patients with acute head injury who require admission and observation within hospital [7].

CT scans aids in examination using bone windows for fractures, examination of the tissue windows for the presence of extra-axial hematoma, intra-parenchymal hematoma, or contusions.

CT scans also survey the brain for any evidence of pneumocephalus, hydrocephalus, cerebral edema, midline shift, or compression of the subarachnoid cisterns at the base of the brain [7].

In 2007, Schneider et al., reported a systematic review about neuroendocrine dysfunction following subarachnoid hemorrhage and traumatic brain injury between 2000 and 2007 including 19 studies and 1137 patients [3].

They reported the pooled prevalence of hypopituitarism in the chronic phase after traumatic brain injury and aneurysmal subarachnoid hemorrhage were (27.5%).

Based on data in the current literature, approximately 15%-20% of TBI patients develop chronic hypopituitarism, which clearly suggests that TBI-induced hypopituitarism is frequent in contrast with previous assumptions [1].
The change in prevalence of Hypopituitarism following traumatic brain injury is questioned by Kokshoorn NE et al., in 2010 and the authors answered this question based on the hypothesis that the prevalence is affected by the use of different dynamic tests and different normal values [8].

Our analytical prospective study included 23 patients collected from the Emergency and Trauma Unit at Neurosurgery department in Cairo university hospitals with history of trauma from December 2020 to April 2021 with our inclusion criteria.

In our study the sample size was 23 which is comparable to other studies. F. Tanriverdi et al., reported a review of 16 studies done from 2004 to 2009 with some studies having a much lower sample size e.g 18 patients [9], 23 patients [10] and 50 patients [11] and on the other side studies with a larger number e.g 170 patients reported by Leal-cerro [12].

In most studies mentioned in literature, they samples were taken from patients whether symptomatic or not. Leal-cerro reported cross-sectional study started with a questionnaire and involved only patient that may have symptoms suggestive of endocrine dysfunction [12].

Out of 23 patients included, 6 patients (26%) had pituitary dysfunction and that number is not different from most numbers reported in literature. The estimated pooled prevalence in 16 studies in systematic review was 15-28% [13].

In our study, we used the primary tests to detect hormonal deficiencies i.e ACTH, morning cortisol, TSH, LH, FSH, GH and due to limited resources and unavailability of tests most of times dynamic tests were not used in our study.

The use of dynamic tests was not a point of consensus in previous studies published in literature.

In their systematic review, F. Tanriverdi et al., reported 4 studies using dynamic tests as a confirmation for GH deficiency i.e GH stimulation tests with Arginine, L-dopa and Glucagon [14-17] and 2 studies that used dynamic tests for ACTH and Cortisol deficiency i.e ACTH test, Glucagon stimulation test and CRT test [14,16].

M. Elamin et al., conducted a systematic review and meta-analysis about the accuracy of diagnostic tests for GH deficiency in adults; 15 studies assessed the diagnostic accuracy of the serum IGF1, 6 the GHRH Carginine stimulation test (AST), 3 the ITT, 3 the serum GH levels, two the GHRP6, two the GHRH+GHRP6 two the GHRH + pyridostigmine, two the GHRH stimulation test, one the acipimox + GHRH test, one the hexarelin stimulation test, one the GHRHCGHRP2 test one the GHRHC clonidine test, one the AST, one the glucagon stimulation test, and one the GHRH + somatostatin (SMS) test [18].

They reported the Insulin tolerance test (ITT) with the highest sensitivity 95% and specificity 89% followed by GHRH + Arginine with sensitivity 73% and specificity 81%.

The IGF-1 level came with much lower sensitivity 72% and specificity 63% [18].

In our study, the prevalence of hormonal deficiencies was found near that mentioned in literature. out of 23 patients we diagnosed 2 patients (8.7%) have GH deficiency, 2 patients (8.7%) with ACTH/cortisol deficiency, 1 patients (4.35%) with LH deficiency and 1 patients (4.35%) with TSH deficiency.

In the systematic review, GHD with ACTH were found to be the most common deficit, with a prevalence of 8.7%, LH/FSH (4.35%), and TSH (4.35%) deficiencies [1].

In our study; 23 patients included, 11 patients (47.8%) had moderate head injury and severe for the rest 12 patients (52.2%).

In the literature, there is diversity regarding the GCS of patients included in the study with 2 studies by Herrmann and Leal-cerro included only patients with GCS less than or equals 8 i.e only severe head injury [12,19] four cross sectional studies reported by Agha, popovic and Srinivasan, included only patients with GCS less than or equals 13 i.e moderate head injury [14,20,21].

In our study we follow-up patients from 24 hours from trauma to at least to 2 month, we only insisted on the minimum of 2 months.

Unlike other studies in literature like Leal-cerro and Kokshoorn who recruited patients with trauma occurred at least one year ago [10,12].

Kleindienst et al., included patients in acute phase and after 2 years from trauma [10].

The most of studies included patients with trauma at least 3 month and up to 12 months [1,3,16,21,22] 24 months (14) and 30 months (23) from trauma.

Most patients (71%) reported by Benvenegaet al., [13] were diagnosed with hypopituitarism within 1 yr of injury. However, both reviews indicate a
substantial number of patients were diagnosed many years after injury.

As pointed out, the symptoms of hypopituitarism may erroneously be “ascribed to the post-concussion syndrome and are often ignored for many years” [24].

The delay in diagnosis of these patients occurred despite the fact that they suffered fully developed hormonal deficiencies with overt clinical manifestations. GHD or partial deficiency of other pituitary hormones as found in the present study is typically less obvious, and recognition of these deficiencies may be obscured more easily by the physical, cognitive, and psychosocial sequelae of traumatic brain injury [25].

Until recently, neuroendocrine dysfunction after TBI was thought to be an uncommon disorder, with only approximately 367 cases of TBI-induced hypopituitarism reported before 2000 [13].

After that a lot of studies done and systematic review revealing underestimating of that diagnosis among Brain injury patients.

The prevalence of pituitary hormonal imbalance found in our study is 26% which is coincident with other studies mentioned in literature.

Most important points interpreted in our study:
- There is a relationship between severity of trauma and pituitary hormonal imbalance as the more severe the head injury the more likely hormonal affection occur.
- This is made clear as (66.6%) 4 patients affected out from 12 with severe head trauma and in case of moderate head injury we found (33.3%) 2 patients affected out from 11.
- Imaging of all cases diagnosed with hormonal imbalance showed frontal, temporal or manifestations of skull base affection.
- Pituitary hormonal imbalance more common in males than females.
- However, there are some limitations for our study for example:
  - Limited time as we have extra 4 patients that developed symptoms suggestive of hormonal imbalance after we finished the two months of follow-up in our the study.
  - Also limited resources as we could not perform dynamic tests in the study to diagnose ACTH and Growth deficiency.

Conclusion:

Pituitary hormonal imbalance is one of the long term sequelae of Traumatic Brain injury. Many patients are under-diagnosed because symptoms of mild hypopituitarism are slowly developing. Growth hormone an ACTH are the most frequent pituitary hormone deficiencies in patients who have sustained TBI.

This should not be underestimated because hormonal abnormalities may contribute to a diminished quality of life.

Adequate history taking putting in mind symptoms suggestive of hormonal deficiencies is the key for Adequate Diagnosis and Management.

References


تحليل مرجعي لنتائج التدخل الجراحية الأمامية والخلفية المشترك في علاج إصابات الفقرات العنقية ما بين الفقرة الثالثة والسابعة

لا تزال كسور الفقرات العنقية ما بين الثنائية والسابعة مشكلة شائعة. غالباً ما ترتبط هذه الإصابات بالعجز وعدم القدرة على الحركة حيث أنها تؤدي إلى عدة أضرار بالنية التشريحيّة للرقية، بما في ذلك الكسور، وتعزر الأربطة، تمزق الفضائي، وغالباً ما يصاب الجبل الشوكي العنقية وتجدد الأعصاب.

يجب معالجة هذه الإصابات جراحياً بهدف لمنع تدهور الحالات وتخفيض الضغط عن النخاع الشوكي للحفاظ على قدرة المرضى على الحركة.

أفاد العديد من البحاث عن المرضى الذين خضعوا لعمليات من أجل تخفيف الضغط الأمامي والخلفي، لكنهم لم يرقعوا بين النتائج للتدخل الأمامي أو الخلفي فقط أو التدخل المشترك من الأمام والخلف.

اشتملت الدراسة على 40 مريضاً تم جرحهم في وحدة الطوارئ بقسم جراحة إن للمرضى بجامعة القاهرة في الفترة من 2016 إلى 2018 وخصصوا لهذا الإجراء.

أظهرت الدراسات أن المرضى تحسن كامل في القدرة على الحركة وباقي المرضى أظهروا تحسن جزئي وخرج جميع المرضى من القسم وتم متابعتهم بشكل منتظم بالعيادات.

يوفر التدخل الجراحي المشترك في تثبيت الفقور العنقية من الأمام والخلف الاستقرار والاندماج المحبط في كسور العقد الفقري العنقية ويعد فرصة لإزالة الضغط على النخاع الشوكي من الخلف والأمام مما يوفر نتائج جيدة في المحادثة والاندماج والتعافي السريع، ولم تتمكن من العثور على أي مواد مطابقة لهذا الإجراء دراستنا عدد ديسمبر/2012.