Evaluation of pituitary function in cases with the diagnosis of pediatric mild traumatic brain injury: Cross-sectional study

Hakan Aylanç, Filiz Tütüncüler¹, Necdet Süt²

Departments of Pediatrics, ¹Pediatric Endocrinology and ²Biostatistics and Medical Informatics, School of Medicine, Trakya University, Edirne, Turkey

ABSTRACT

Background: This study was to determine whether pituitary dysfunction occurs after head trauma in children or not and which axis is affected more; to define the association of pituitary dysfunction with the severity of head trauma and duration time after the diagnosis of head trauma. Materials and Methods: In this study, 24 children who were diagnosed with head trauma were evaluated regarding pituitary dysfunction. In all cases, after 12 h fasting, serum cortisol, fT3, fT4, thyroid-stimulating hormone, prolactin, insulin-like growth factor-1, serum sodium, urine density, follicle-stimulating hormone, luteinizing hormone, in female cases E₂, in male cases, TT levels were determined. Results: Mean age of children was 9.5 ± 3.1 years, 14 children (58.3%) had mild, 9 children (37.5%) had moderate, and 1 children (4.2%) had severe head trauma according to the Glasgow coma scale. Mean duration time after head trauma was 29.4 ± 9.8 months. In all cases, no pathologic condition was determined in the pituitary hormonal axis. In one children (4.2%), low basal cortisol level was found. There were no children with hormonal deficiency in this study. Conclusion: Although pituitary dysfunction after head trauma may develop in the early period, some may present in the late period; therefore, all cases should be followed up at outpatient clinics for a longer period.

Key words: Child, head trauma, pituitary dysfunction, traumatic brain injury

Introduction

Children and infants suffer from head trauma more than adults because of having heavier heads with respect to their bodies and weaker muscles. In childhood, a mild brain injury may affect language development, cognitive functions, and learning in the long term.¹

The annual hospitalization incidence for traumatic brain injury (TBI) is in a wide range of 70–294/100,000 for children and adolescents, and this rate is determined to be 150/100,000 for population of 0–15 years. The diagnosis period of hypopituitarism in children ranges from the 1st week of TBI to 16 years after head trauma.²⁻⁵

The numbers of publications reporting that functional disorders of the pituitary, like early puberty, or pituitary insufficiency develop after head trauma in the childhood period are continually increasing.⁶⁻¹¹ The most frequent pituitary function disorders developing after head trauma are growth hormone deficiency (GHD) and gonadotropin deficiency.¹² Based on these study results, a consensus report was published aiming to identify pituitary function disorders that may develop after head trauma in the early period, to start these cases on replacement therapy, and increase the quality of life.¹³

Address for correspondence:
Dr. Hakan Aylanç, Department of Pediatrics, School of Medicine, Trakya University, Edirne, Turkey.
E-mail: draylanc@hotmail.com

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To understand the natural history of TBI-induced hypopituitarism in childhood, prospective studies are warranted, but there are insufficient prospective studies, although the head injury is common in the pediatric population. The normal pituitary functions, especially GH, and thyroid and gonadal axis are necessary for growth and pubertal maturation in childhood. Hence, hormonal dysfunction following TBI might affect children more severely than adults.\textsuperscript{[11]}

In our study, we undertook a cross-sectional evaluation to assess the chronic period results regarding pituitary insufficiency of pediatric patients with TBI.

**Materials and Methods**

In this cross-sectional study, 24 pediatric patients who applied to Trakya University, Medical Faculty, Pediatric Health and Diseases Department, Pediatric Emergency Department between April 2006 and December 2008 with head trauma, diagnosed with TBI were enrolled.

The inclusion criteria for the study were determined as age between 5 and 17 years, with diagnosis of head trauma treated at Trakya University, Medical Faculty, Pediatric Health and Diseases Department Pediatric Emergency Unit, Glasgow coma scale (GCS)\textsuperscript{[10]} of 13 or below, or GCS 13–15 and pathology on computed brain tomography (CBT). Exclusion criteria were long-term medication use (steroids, anti-epileptics, etc.), syndrome/chromosomal anomalies/developmental defects of the central nervous system or previous infection or metabolic disease or previous diagnosis of head trauma. The families of the patients were reached and called in.

The ages, type of trauma, severity of head trauma, duration and style of treatment, laboratory tests (especially imaging methods and findings on images), the duration from diagnosis to the time of the study was identified and complaints during this time, physical examination findings at the time of the study, and assessment of basal hormone tests related to pituitary functioning were recorded in detail.

The study was supported as a Trakya University Scientific Research Project. Before the study permission was granted by Trakya University Medical Faculty Ethics Committee. In addition, the patients and parents participating in the study signed an informed consent form.

**Assessment of cases**

All cases included in the study were given an appointment and examined by the same clinician at Trakya University, Medical Faculty, Health Administration and Research Center, Pediatric Endocrinology Clinic.

All cases provided a detailed history. Findings that may indicate pituitary function disorders after head trauma, especially, (weight gain or loss, lethargy, tiredness, headache, chills, reduction in success in school, etc.,) were questioned in detail.

The physical examination assessed the anthropometric parameters (weight, height), blood pressure, and pubertal development of cases. The height of patients was measured with no shoes on using a Harpenden stadiometer mounted on the wall (Holtain Limited, UK); weight was measured in the morning on an empty stomach in light underwear on a scale (Seca 703, accurate to 100 g, Seca GmBH, and Co. KG; Hamburg, Germany). Blood pressure measurements were the average of 3 measurements taken using a sphygmomanometer appropriate for age and arm size.

To evaluate puberty, the staging system of Marshall and Tanner was used.\textsuperscript{[15,16]} For boy’s testes ≥ 4 ml and girls breast budding (M2) were accepted as entry into puberty.

**Obtaining and examining blood and urine samples**

All cases had basal cortisol, free T3, free T4, thyroid-stimulating hormone (TSH), prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone in boys and estradiol in girls (UniCel Dxi 800, Beckman Coulter, USA), Insulin-like growth factor-1 (IGF-1) (Immulite-2000, Siemens Healthcare Diagnostics, UK), and serum sodium (Siemens Advia\textsuperscript{®} 1800 Chemistry System, Siemens Advia, Japan) measured in blood taken in the morning from 08.00 to 09.00 after 12 h fasting. Urine density (CombiScreen\textsuperscript{®} 11YS Plus, Analyticron Biotechnologres AG, Germany) was measured in a morning urine sample. To check pituitary hormones together with basal tests, it was planned that cases with pituitary axis disorders found after basic tests be given the necessary stimulation tests (if cortisol was low adrenocorticotropic hormone [ACTH] stimulation test, if fT4 and TSH were low TRH test, etc.,) to determine which axis the hormonal disorders were on. Basal cortisol levels of < 5 µg/dl were accepted as suspected ACTH deficiency and it was planned that these cases have ACTH stimulation tests. The cases were divided into two groups according to the severity of head trauma as mild or moderate and compared regarding anthropometric and hormonal assessments.

The IGF-1 Z-scores of patients were calculated according to the age of patients and puberty circumstances. For IGF-1 Z-score calculation, the formula recommended for
Turkish children was used; IGF-1 Z-score = (√IGF-1-[β × age (years)+ α])/SD.\(^{[17]}\)

The statistical analysis of the results obtained in the study was completed using the STATISTICA® 7.0 (Stat Soft Inc., Tulsa, USA) (SN: AXF003C775430FAN2) program at Trakya University Medical Faculty Biostatistical Department. The numerical values of results are expressed as mean ± standard deviation (SD). A \(P < 0.05\) was accepted as significant. To identify whether significant correlations exist between selected variables, the Spearman correlation analysis was used. To compare the results of cases classified as mild or moderate regarding severity of trauma, the Mann–Whitney U-test was used. As there was 1 case classified as severe, comparisons were made between the moderate and mild groups.

### Results

A total of 24 cases were included in the study. Of cases, 16 were male (66.7%), and 8 were female (33.3%). The mean decimal age was 9.5 ± 3.1 years. Fourteen cases (58.3%) were prepubertal, and 10 (41.7%) were in the pubertal period. According to the GCS, 14 cases (58.3%) were classified with mild, 9 cases (37.5%) were moderate, and 1 case (4.2%) had severe head trauma. As there was only 1 case in the severe head trauma group, this case was included in the moderate group for comparisons. When the duration since the trauma was investigated, it was at least 12 months, at most 44 months, with an average of 29.38 ± 9.75 months. Apart from one patient, the CBT at the time of diagnosis showed pathological findings. The general characteristics of cases are given in Table 1. When the weight and height SD values are examined, none of the cases were found to have short height or low weight [Table 2]. The IGF-1 values of cases were within normal limits. When the IGF-1 Z-scores are assessed according to the Tanner puberty stages, 8 pubertal and 1 prepubertal cases, a total of 9 (37.5%) cases were identified as below −2 SD. However, none of these cases had short height [Table 2]. It was planned to decide whether to complete dynamic stimulation tests regarding GHD to monitor the growth speeds of cases. When the IGF-1, IGF-1 Z-score, and height SD score (SDS) are compared between the mild and moderate TBI groups, there was no significant difference found [Table 3].

When the basal cortisol taken from patients in the morning was investigated, two cases had low basal cortisol values identified. To assess whether these patients had secondary adrenal insufficiency, a low dose (1 mcg) ACTH stimulation test was planned. A low dose (1 mcg) ACTH stimulation test was completed for one case with basal cortisol below 5 ug/dl. The basal ACTH levels and cortisol levels after stimulation (18.44 ug/dl) were normal for the case tested. There was no statistically significant relationship found between basal cortisol values and GCS points (\(P = 0.097\)). The mean basal cortisol in the patients with moderate TBI

### Table 1: General characteristics of the patients

| Characteristics                  | N/mean±SD |
|----------------------------------|-----------|
| Case number (n)                   | 24        |
| Age (decimal year)               | 9.5±3.1   |
| Gender (female/male)             | 8/16      |
| Puberty (n)                      |           |
| Prepuberty                       | 14        |
| Puberty                          | 10        |
| GCS                              |           |
| ≥13                              | 14        |
| 9-12                             | 9         |
| ≤8                               | 1         |
| CT pathology                     |           |
| Yes                              | 23        |
| No                               | 1         |
| Weight SDS                       | –0.016±0.85 |
| Height SDS                       | –0.059±1.10 |
| Time after TBI (month)           | 29.38±9.75 |

SDS: Standard deviation score, TBI: Traumatic brain injury, GCS: Glasgow coma scale, CT: Computed tomography

### Table 2: Patient demographic characteristics

| Case number | Gender | Decimal age | Tanner puberty stage | Height SDS | Weight SDS | Time after TBI (months) |
|-------------|--------|-------------|----------------------|------------|------------|-------------------------|
| 1           | Female | 6.99        | 1                    | 1.62       | 0.13       | 21                      |
| 2           | Male   | 14.31       | 4                    | 1.1        | 0.76       | 29                      |
| 3           | Male   | 11          | 2                    | –1.14      | 0.58       | 19                      |
| 4           | Male   | 10.29       | 1                    | 1.48       | 0.76       | 21                      |
| 5           | Female | 6.25        | 1                    | –0.21      | –0.06      | 30                      |
| 6           | Male   | 16.05       | 4                    | 1.07       | 2.46       | 27                      |
| 7           | Male   | 12.34       | 2                    | 0          | –0.18      | 43                      |
| 8           | Male   | 14.24       | 3                    | –1.1       | –1.38      | 26                      |
| 9           | Male   | 7.48        | 1                    | –1.73      | –1.10      | 12                      |
| 10          | Male   | 9.42        | 1                    | 0.08       | 0.02       | 31                      |
| 11          | Female | 7.9         | 1                    | 1.06       | 1.37       | 21                      |
| 12          | Female | 12.49       | 4                    | 0.05       | –0.24      | 31                      |
| 13          | Male   | 10.49       | 2                    | –1.72      | –0.27      | 33                      |
| 14          | Male   | 11.98       | 2                    | –1.16      | –0.65      | 19                      |
| 15          | Male   | 5.93        | 1                    | –0.12      | –0.15      | 19                      |
| 16          | Male   | 6.23        | 1                    | 1.06       | –0.20      | 23                      |
| 17          | Male   | 8.74        | 1                    | 0.76       | 0.56       | 44                      |
| 18          | Female | 7.43        | 1                    | –1.44      | –0.77      | 17                      |
| 19          | Female | 5.21        | 1                    | 0.44       | 0.22       | 36                      |
| 20          | Male   | 7.28        | 1                    | –0.54      | –0.46      | 42                      |
| 21          | Female | 6.53        | 1                    | 0.18       | –0.67      | 43                      |
| 22          | Male   | 6.65        | 1                    | –0.78      | –0.22      | 44                      |
| 23          | Male   | 9.95        | 2                    | 1.42       | 0.39       | 36                      |
| 24          | Female | 13.14       | 4                    | –1.78      | –1.28      | 38                      |

SDS: Standard deviation score, TBI: Traumatic brain injury
was lower than the mild group. However, this difference between the two groups was not found to be statistically significant ($P = 0.1$). Although there was a negative relationship observed between the duration since trauma and basal cortisol, this finding was not statistically significant ($P = 0.252, r = -0.246$) [Figure 1].

The fT3, fT4, and TSH values of all cases were within normal limits. There was no significant difference found in a comparison of thyroid hormone levels between the mild and moderate TBI groups [Table 3].

The LH and FSH values of 10 (41.7%) pubertal patients were at pubertal levels while they were at low levels for 14 (58.3%) prepubertal patients and these results are in accordance with the findings from the physical examination. Of the 10 pubertal (41.7%) cases, 2 were female, and 8 were male. The gonadotropin values were FSH 3.68 ± 2.15 mIU/ml, and LH 2.89 ± 2.5 mIU/ml in the cases who had entered puberty according to the physical examination ($n$: 10). The total testosterone level in the 8 male pubertal patients was 1.29 ± 1.27 ng/ml. No patient was identified with delayed or early puberty.

The serum PRL levels of all patients were normal. There was no difference found in PRL levels between cases with mild and moderate TBI [Table 3].

The mean serum sodium level of cases was 137.3 ± 1.8 mEq/L and no patient had hypernatremia or hyponatremia. The mean urine density of morning samples was 1020.4 ± 4.4. There was no case with urine density <1010. According to the serum sodium and urine density findings, no systolic dyssynchrony index case was identified. There was no difference between the mild and moderate TBI groups regarding serum sodium and urine density [Table 3].

There was no correlation found between IGF-1 Z-score values and duration since trauma ($P = 0.468$), GCS ($P = 0.811$), basal cortisol ($P = 0.064$), and severity of trauma ($P = 0.996$).

### Discussion

Although pituitary function disorders after trauma were described nearly a century ago, until recently, a limited number of studies had been published. The relationship between TBI and pituitary insufficiency was first described by Cyran in 1918.[18] However, as TBI patients were not assessed from an endocrinological point of view in the acute and long-term, this situation has not been sufficiently explained in the intervening century. In addition to pituitary function disorders after pediatric head trauma, such as early puberty, the studies reporting the development of hypopituitarism are increasing.[6-11] Kelly et al. predicted that GCS below 10 and widespread brain edema on the first CBT/magnetic resonance with hypotensive/hypoxic injury findings were significant precursors to TBI-induced hypopituitarism.[19] Based on these findings, they emphasized that in children if care is taken about hypopituitarism after TBI, they will have the best chance of healing.[20] The duration between TBI-induced hypopituitarism diagnosis varied from 5 months to 15 years and from 1 month to 23 years.[30,21] According to data from broad prospective studies, early endocrine abnormalities may be temporary. As a result,
they should be reassessed during TBI rehabilitation and 1 year after TBI.[22,23]

In recent years, retrospective studies of the adult patient group with TBI have found the incidence of TBI-induced hypopituitarism between 28 and 68.5%. A study of the pediatric period found a 60% rate of TBI-induced hypopituitarism.[28] A retrospective study, by Aimaretti et al., assessed patients 3 and 12 months after TBI and found 40% of patients had normal pituitary functioning 3 months later while 60% had normal functioning at the end of the 1st year.[29] Of patients with normal pituitary functioning in the 3rd month, 5.5% had developed pituitary hormone deficiency at the end of the 1st year. Ulutabanca et al., in a prospective study, of 41 children with TBI found that in the early period 10 had ACTH deficiency, 7 had TSH deficiency, and in the 12th month, 2 had GHD and 1 had ACTH deficiency.[11] In our study, while the period since trauma varied from at least 1 year to nearly 4 years, none of our cases had pituitary function disorders identified. The reason for this result, different to the literature, may be linked to the low number of cases in our study group or another reason may be the possibility that temporary function disorders that occurred in the acute period after TBI may have resolved. In addition, the fact that our cases had mild or moderate TBI may have affected the results.

To date, the studies related to TBI-induced hypopituitarism have found deficiency of GH most frequently among anterior pituitary hormones. Due to the localization of growth hormone-releasing hormone neurons in the hypothalamus, it is vulnerable to vascular injuries. In addition, the somatotrophs are in the lateral part of the anterior pituitary and are thought to be primarily injured due to the vulnerable vascular structure of the long pituitary portal system.[27] A prospective pediatric study found GHD in the acute phase, however in the chronic phase, 2 cases (9.1%) had GHD.[11] A study of adult patients with hormonal assessment in the 3rd month after TBI found severe GHD at a rate of 25%.[29] Different studies of adults using dynamic GH stimulation tests found this rate varied from 10 to 25%.[19,25,27,28] In general, although GHD is most frequently found reported to TSHIB; in our study, we did not identify any case with short height and GHD. The weight and height SDS values of cases were within normal limits. However, when the IGF-1 Z-scores of cases are evaluated according to the study by Bereket et al., 9 cases were seen to be below −2 SD.[10] Of these cases, 8 were in the pubertal period. As the study was cross-sectional, these cases were assessed for the first time. Histories did not describe any cessation of growth after TBI and as the height SDS values were above −2 SD, these cases were not assessed as short height. However, as these cases were a group that may have potential GHD, their yearly growth rate was to be monitored by a nearby clinic.

After TBI, gonadotropins are the second most frequently affected after GH. A variety of studies has published temporary gonadotropin deficiency.[22,29-31] A study found that 6 months after TBI gonadal functions resolved without intervention.[31] This situation is thought to be linked to the suppression of the hypothalamic-pituitary-gonadal axis to reduce energy consumption during the acute disease.[32] Kelly et al. used GnRH tests to assess gonadal functioning and found 4 out of 18 males and 1 in 4 females had insufficient responses.[19] Poomthavorn et al., in a study of 117 children with severe head trauma found during observation that a patient with TBI at 3.3 years developed central early puberty at 7.7 years.[32] Benvenega et al. reported that in 4 cases with central hypothyroid diagnosis after TBI in the childhood period, gonadotropin deficiency developed 5–42 years later.[33] Miller et al. showed that in 3 cases with TBI during infancy, 12 years later multiple pituitary hormone deficiency including gonadotropin deficiency had developed.[34] Another study showed 1 patient had gonadotropin deficiency in the acute period, and on long-term monitoring, no case with gonadotropin deficiency was identified.[11] In our study, there was no case in the pubertal period with delayed puberty. In addition, we did not find any case with early puberty. In the literature, gonadotropin deficiency may develop many years later, so it is necessary to provide long-term clinical monitoring of TBI patients.

Cortisol has vital importance as if patients with subclinical cortisol deficiency after TBI are exposed to stress they may develop adrenal crisis. As a result, early diagnosis of cases with cortisol deficiency is important. Between 1976 and 2006 in the literature, a total of 11 (55%) patients with ACTH deficiency linked to TBI were published.[6] A prospective study published by Cohan et al. found 53% of 80 patients with moderate or severe TBI in the young adult period had adrenal insufficiency.[35] Agha et al., in a broad series study, compared the daily cortisol profile of patients with partial ACTH deficiency and hypopituitarism under stress-free conditions with a healthy control group and found similar results.[18] At the end of the study, they recommended a lower dose therapy than the normal standard dose for subclinical patients or medication-free monitoring.[18] In a study of adult TBI patients by Tanriverdi et al., in the 5th year, 4% of patients had ACTH deficiency.[36] In a prospective study of pediatric patients, in the acute period, 10 out of 41 patients had temporary ACTH deficiency while in the long-term 1 patient had ACTH deficiency.[11] Barton
et al. showed there was a positive correlation between the cortisol levels of patients with mild and moderate TBI and the severity of traumatic damage.\cite{37} In our study, we identified 2 cases with low basal cortisol. One of these cases refused ACTH tests while 1 case did the test and obtained normal results. In addition, although the basal cortisol values were observed to have a negative relationship with duration since TBI, this finding was not statistically significant.

Thyroid hormones are shown to be less affected by TBI than other anterior pituitary hormones.\cite{6,28} Thyrotropes are found in the more interior parts of the adenopituitary and as the pituitary veins are short, are in a protected situation. Compared to other sections of the frontal lobe, they are exposed to less traumatic damage. The short pituitary veins are mainly fed by the long pituitary veins which are more vulnerable to injury.\cite{38} In addition to the anterior pituitary hormone deficiencies related to TBI, TSH deficiency is variable. A prospective pediatric study found TSH deficiency in 7 patients out of 41 in the acute period; however, it was shown that this deficiency did not continue in the chronic period.\cite{11} Kelly et al., in a study, of 22 patients with TBI found insufficient response to the TRH stimulation test in only 1 (4.5%) patient with low T4 and TSH levels.\cite{19} A study by Lieberman et al. found that 11.6% of patients without high thyrotropin had low fT4 and TSH insufficiency.\cite{21} In our study, we did not find any patients in the chronic period with TSH deficiency.

Although traumatic brain damage can cause hyperprolactinemia, hyperprolactinemia in the pediatric period is rare in patients with TBI and generally temporary.\cite{38,39} However, in adults, more than 50% of patients have hyperprolactinemia in the early period after TBI.\cite{9,40,41} Recently, a study by Niederland et al., of 26 child patients found only one with high PRL (hyperprolactinemia).\cite{23} In our study, no case was identified with hyperprolactinemia. As the cases included in the study were not monitored in the acute period, the lack of identification of high PRL in the advanced period does not mean that hyperprolactinemia did not occur in the early period. As a result, it was not possible to identify whether hyperprolactinemia developed in patients after TBI.

The incidence of central diabetes insipidus (CDI) is observed in the early period after TBI and is reported to resolve in the advanced period.\cite{40} In the pediatric age group, CDI developing after TBI was reported in 3 cases in a case report by Mariani et al.\cite{41} A study investigating 70 adult patients with TBI evaluated in the 3\textsuperscript{rd} and 12\textsuperscript{th} month found the DI rate in the early period clearly reduced.\cite{23} After TBI permanent, CDI was found to be related to the severity of head trauma and low GCS points.\cite{6,42} In our study, the CDI was assessed from the patients histories, urine density, and serum sodium levels and no finding leading to consideration of CDI was identified. In our study, TBH was not assessed in the early period as this was a cross-sectional study and as stated in the literature CDI may be temporary, so we cannot comment on whether it occurred or not.

In studies, attempts have been made to identify findings with correlations to GCS. In only one study was a positive correlation shown between GCS and TBI-induced hypopituitarism.\cite{24} Other studies have not shown this relationship.\cite{6,12} In our study, similar to other studies, no significant relationship was found between GCS and TBI-induced hypopituitarism.

Conclusion

In this study, assessing the pituitary function in the advanced period of a small but sufficient number of children with head trauma, though the duration since trauma varied from 12 to 44 months, no pituitary hormone deficiencies supported by clinical and laboratory work were identified. However, if considered from the aspect of GHD in our cases, though height SDS was normal, the IGF-1 Z-score levels were low, and the growth rates of these children should be monitored in the long term and if insufficient GH stimulation tests might be necessary. At the time of the study, no pituitary functional problems were identified, but monitoring of TBI cases at certain intervals for pituitary functioning is important for early diagnosis and treatment. Informing both pediatric clinicians and brain surgery experts about pituitary function problems after head trauma is another factor in early diagnosis and treatment.

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Conflicts of interest

There are no conflicts of interest.

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