Dysfunction of hypothalamic-hypophysial axis after traumatic brain injury in adults

Clinical article

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Object. Traumatic brain injury (TBI) is a major cause of serious morbidity and mortality. The incidence is 100–500/100,000 inhabitants/year. Chronic pituitary dysfunction is increasingly recognized after TBI. To define the incidence of endocrine dysfunction and risk factors, the authors describe a prospectively assessed group of patients in whom they documented hormonal functions, early diagnosis, and treatment of neuroendocrine dysfunction after TBI.

Methods. Patients aged 18–65 years were prospectively observed from the time of injury to 1 year postinjury; the Glasgow Coma Scale score ranged from 3 to 14. Patients underwent evaluation of hormonal function at the time of injury and at 3, 6, and 12 months postinjury. Magnetic resonance imaging was also conducted at 1 year postinjury.

Results. During the study period, 89 patients were observed. The mean age of the patients was 36 years, there were 23 women, and the median Glasgow Coma Scale score was 7. Nineteen patients (21%) had primary hormonal dysfunction. Major deficits included growth hormone dysfunction, hypogonadism, and diabetes insipidus. Patients in whom the deficiency was major had a worse Glasgow Outcome Scale score, and MR imaging demonstrated empty sella syndrome more often than in patients without a deficit.

Conclusions. To the authors’ knowledge, this is the third largest study of its kind worldwide. The incidence of chronic hypopituitarism after TBI was higher than the authors expected. After TBI, patients are usually observed on the neurological and rehabilitative wards, and endocrine dysfunction can be overlooked. This dysfunction can be life threatening and other clinical symptoms can worsen the neurological deficit, extend the duration of physiotherapy, and lead to mental illness. The authors recommend routine pituitary hormone testing after moderate or severe TBI within 6 months and 1 year of injury. (DOI: 10.3171/2009.10.JNS09930)

**Key Words** • traumatic brain injury • hypopituitarism • hypothalamic-hypophysial axis

Traumatic brain injury is a major cause of serious morbidity and mortality. The incidence is 100–500/100,000 inhabitants/year. The aftereffects on survivors of TBI vary from physical handicaps to long-term cognitive, mental, and social problems. Posttraumatic hypopituitarism is significant. Current observation of adult patients after TBI has shown that > 30% have a disorder of at least 1 endocrine function (most often gonado- and somatotropins), but a combined deficit is more rare.1–8,18,20–22 In contrast to studies in adults, only case reports about posttraumatic hypopituitarism in children have been published. These reports mainly describe the pubertal disorder and growth hormone dysfunction with no overview of symptomatology. Neuroendocrine disorders can threaten the patient’s quality of life with a chronic neurological deficit; apathy, fatigue, and many other clinical symptoms can worsen the deficit, extend the duration of physiotherapy, and cause mental illness.8,15,16,17,19

Hormonal dysfunction can be acute and it can also be seen up to 10 years postinjury. In 70% of the patients it occurs during the 1st year after TBI. Some of the deficits can be transitory. Clinical symptoms are affected by the type of neuroendocrine dysfunction, its relevance, and the speed at which it develops. Therefore, the clinical symptoms vary. The age of the patient is significant as well. In general, a serious hormonal disorder is not difficult to diagnose, but a partial deficiency is harder to isolate.

The pathophysiology of posttraumatic endocrine...
dysfunction is unclear. There is no clinical-pathological correlation (negative CT or MR imaging findings, for example, do not exclude a disorder) and the risk factors are controversial. In the pathogenesis of the disorder, not only is primary brain injury with bleeding edema important, but secondary injury is as well. Secondary injury arises in the hours and days after TBI, the result of rising transmitter substances of inflammation (amino acids, free radicals, and nitric oxide), excitatory amino acids (N-methyl-D-aspartate), and interleukin-6 in response to increased intracranial pressure and brain hypoxemia.\(^8,10,11,13,14,22\) Although the primary insult cannot be avoided, the secondary processes can be by using modern treatment methods.

The present project is based on the prospective observation of hormonal function in adults after TBI, early diagnosis, and treatment of neuroendocrine dysfunction after TBI. We also attempted to quantify the frequency of hypothalamic-hypophysial disorder after TBI and the identification of risk factors.

**Methods**

Patients ranged in age from 18 to 65 years. They had sustained moderate or severe TBI, and their GCS scores ranged from 3 to 14. After providing informed consent (if possible), they were admitted to the ICU of the neurosurgery department, where their status was stabilized, or, if necessary, an operation was performed. Subsequently, their hormonal functions were observed in the acute phase and 3 months in our department, and at 1 year with endocrinology specialists. Patients were divided into 3 groups according to their GCS score: mild,\(^13,14\) moderate,\(^9–12\) and severe.\(^3–8\) Patients with cancer, preexisting hormonal insufficiency, or those receiving glucocorticoids within 2 months of injury were excluded.

**Examination Methods for Adult Patients**

We used the following protocols for examining adult patients who had sustained TBI.

**Acute Stage of TBI.** We monitored morning cortisol, adrenocorticotropic hormone, Na, K, Cl, osmolarity of blood and urine, water balance, TSH, and FT4.

**At 3–6 Months After TBI.** We monitored morning cortisol, TSH, FT4, insulin-like growth factor–1, testosterone, and sex hormone–binding globulin in men and anamnesis of menses in women of childbearing age. In cases of dysfunction, we assessed luteinizing hormone, follicle-stimulating hormone, estradiol, and prolactin. If there was any dysfunction (polydiabetes), we measured Na, K, Cl, osmolarity of blood and urine, and water balance.

**At 1 Year After TBI.** Morning cortisol, < 500 nmol/L, was tested with analog adrenocorticotropic hormone. We also conducted FT4 and TSH tests. Furthermore, we performed the following assays: dynamic testing with arginine or glucagon to assess stimulation of growth hormone, lipid spectrum, and truncal obesity. In men, testosterone and sex hormone–binding globulin were assessed; in women, anamnesis of menses in those of childbearing age was assessed. In cases of dysfunction, we assessed luteinizing hormone, follicle-stimulating hormone, estradiol, and prolactin. If necessary Na, K, Cl, osmolarity of blood and urine, and water balance were assessed.

The reference ranges are expressed as the 5th and 95th percentiles for healthy men and women. Major hormonal deficiencies were defined, such as a peak cortisol below the 5th percentile, testosterone below the 5th percentile in men, and estradiol below the 5th percentile in women. Growth hormone, after stimulation of arginine, below the 10th percentile and persistent diabetes insipidus were considered a reflection of major hormonal deficiency.

Parameters evaluated included GCS score, length of ICU stay, hypotension, hypoxia, and intracranial pressure (if used).

Computed tomography was performed on admission and also 24 hours after admission. Patients were then divided into 6 groups according to the severity of the CT findings.

**Results**

Overall we included 186 patients in our research. During the acute phase after TBI, 54 patients (29.0%) died. In addition, 13 patients (6.9%) were excluded because they received glucocorticoids, and 1 woman was excluded because she was pregnant. Twenty-nine patients (15%) were lost to follow-up during the observation period. The total number of patients still undergoing observation at 1 year postinjury was 89, making this, to our knowledge, the third-largest study of its kind.

**Acute Phase of TBI**

During the acute phase, we noted a hormonal disorder in at least 1 hormonal axis in 98 (53%) of 186 patients. The hormonal dysfunction was found in somatotropin axis in 36 (37%), gonadotropin axis in 32 (33%), thyrotropin axis in 3 (3%), corticotropic axis in 10 (10%), and the posterior pituitary axis was in 17 patients (17%).

During the acute phase of TBI, 54 patients died, 32 (59%) of whom had some form of hormonal disorder.

**At 3 Months After TBI**

We assessed 118 patients at the 3-month postinjury interval. Forty-four of these patients had a hormonal disorder detected in the acute injury phase, and in 24 (55%) recovery of normal function was documented. We recognized a new hormonal disorder in 7 patients in gonadotropin and thyrotropin axes. We lost 8 patients during this portion of the follow-up period.

**At 6 Months After TBI**

We examined 110 patients, 27 of whom had major hormonal dysfunction noted at the previous follow-up examination. During the last 3 months, hormonal function recovered in another 10 patients (37%), and a newly recognized dysfunction in somatotropin axis was noted in 3 patients. During this portion of the observation period, 21 patients were lost to follow-up.
At 1 Year After TBI

At 1 year we evaluated 89 patients with 20 major hormonal deficits. In 2 patients hormone function recovered and in 1 patient hormone dysfunction in the somatotropin axis was newly recognized. Thus, 19 (21%) patients had major hormonal deficiencies 1 year after surgery. Major deficiencies included growth hormone dysfunction in 12 (63%), hypogonadism in 5 (26%), and diabetes insipidus in 2 (10%).

Summary of Findings

Figure 1 delineates the major hormone deficits at 6 and 12 months postinjury. Tables 1 and 2 provide summaries of 3-month CT findings and 12-month MR imaging findings, respectively.

Of 89 patients with mild, moderate, or severe TBI, 21% had a major hormonal deficit. In the first 3 months after injury, 55% of the patients experienced resolution of their hormonal disorder. In the next 3 months, recovery of normal function occurred in another 8%. During the next 6 months (by the 1-year postinjury examination) recovery of normal function occurred in only 2 patients. In the first 3 months after TBI, a new hormonal disorder developed in 7 patients, and up to 6 months postinjury another 3 patients suffered a newly recognized hormonal dysfunction. Between 6 and 12 months only 1 patient had a newly diagnosed hormonal dysfunction (Fig. 1).

We could identify only 2 significant risk factors from the CT investigations (Table 1). Increasingly, we observed more MR imaging findings of empty sella syndrome in the subgroup of patients with hormonal dysfunction (Table 2). In the subgroup of patient with no hormonal dysfunction, we documented better GOS scores (Table 3). However, this factor was not statistically significant. We believe that early treatment of hormonal disorder can improve patient outcome.

Discussion

Results of previous cohort studies have shown that the most vulnerable parts of the hypothalamic-hypophysial axis are somatotropin and gonadotropin, with incidences of 14–28%. Other parts of hormonal system are affected less frequently.1,4-8,18

Differences between the rates of hormonal disorders in the cohort studies can be explained by the different testing of pituitary function and normal ranges used. In our research, similar to other studies,4-8,18 we observed recovery of hormonal function up to 6 months after TBI in > 50% of patients.

The majority of new hormonal dysfunctions developed within 6 months of injury. The etiological basis of this dysfunction is unknown, but it could be the result of atrophy of pituitary and infundibular structures. We confirmed the presence of this atrophy on MR imaging 12 months after injury, where we also noted a statistically significant increase of empty sella syndrome in the subgroup of patients with hormonal deficits. Previous studies have failed to identify any risk factors leading to hormonal dysfunction. In the present analysis, however, we identified 2 predictors of hormonal dysfunction on CT scanning (Table 1)

Conclusions

The findings of the present study indicate that major hormonal dysfunction develops in approximately 20% of patients after TBI. This dysfunction can be associated with severe TBI on CT scanning. All major changes in hormonal status after TBI, such as recovery of normal function and the discovery of new hormonal dysfunction, appeared within 6 months of injury. Hormonal function changed only in a small number of patients within 6–12 months of injury. Often, we observed empty sella syndrome on MR imaging. This finding could signify atrophy of the pituitary structures. Early diagnosis and treat-
ment of hormonal dysfunction can lead to a better GOS score.

There is a high incidence of major hormonal dysfunction after TBI. Based on our data and those reported in other articles, we recommend routine testing of hormonal functions at 3 and 6 months after TBI and appropriate hormonal replacement therapy.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References