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INVITED REVIEW – OPEN ACCESS

Neuroendocrine Consequences of Traumatic Brain Injury and Strategies for its Management

Aysa Hacioglu[1], Fahrettin Kelestemur[2]

ABSTRACT

Traumatic brain injury (TBI) is a common problem that generally affects the young population. Hypothalamo-pituitary damage may occur as a result of direct damage during trauma or due to secondary insults, such as hypotension or hypoxia that may occur thereafter. The incidence of pituitary dysfunction post-TBI has been reported to range from 5–76.4%. Growth hormone deficiency and central hypogonadism are among the most common hormone deficiencies that occur post-TBI. Patients who develop pituitary dysfunction post-TBI may present with life-threatening hypotension, hyponatremia during the acute phase, or subtle and nonspecific complaints such as fatigue, depression, or cognitive impairments during follow-up. Pituitary dysfunction may recover but new-onset deficiencies may develop over time, mandating routine screening of TBI patients. Several risk factors have been investigated and various screening algorithms have been proposed in recent studies. We aimed to review the recent literature in terms of epidemiology, screening modalities, and clinical perspectives of pituitary dysfunction post-TBI.

Keywords: Diabetes insipidus, hypopituitarism, traumatic brain injury

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[1]Department of Endocrinology and Metabolism, Erciyes University Faculty of Medicine, Kayseri, Turkey
[2]Department of Endocrinology and Metabolism, Yeditepe University Faculty of Medicine, İstanbul, Turkey

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Correspondence
Aysa Hacioğlu,
Erciyes University Medical Faculty, Department of Endocrinology and Metabolism, Kayseri, Turkey
Phone: +90 352 207 66 66/ 20951
e-mail:
aysahadzalic@gmail.com

INTRODUCTION

Traumatic brain injury (TBI) is a common problem that is prevalent worldwide and may cause permanent disabilities and death. It was estimated that one of every 50 emergency department visits (2.2%) occur in consequence of TBI and that 2.2% of all deaths in the United States were TBI-related in 2013 (1). Majdan et al. reported the rate of TBI-related hospital discharge as 287.2:100 000 and the mortality rate as 11.7:100 000 in Europe in 2012 (2). One year later, the same group analyzed the years of life lost (YLL) related to TBI (a measure that is used to estimate the number of years of life lost due to premature death caused by TBI) and reported a total of 374,636 YLLs during 2013 (3). The incidence of TBI and mortality rate was higher among men (3).

The main causes of TBI are listed in Table 1. Falls were the most common cause of TBI, followed by being struck by or against an object, and motor-vehicle crashes in the United States in 2013 (1). The etiology of TBI varies with age; falls were the most common among those aged ≥75 years and between 0–4 years of age and motor-vehicle crashes among 15–24 years of age (1). Falls and traffic accidents were also the most common causes of TBI in Europe with variations across countries (2). One study from our country reported that 20.4% of trauma patients who applied to the emergency department had TBI. The most common cause was traffic accidents, followed by falls. The majority of patients were younger than 50 years and the incidence was higher among men (76%), similar to the results seen in Europe (4).

Neuroendocrine dysfunction secondary to TBI was first recognized in 1918 (5) and there had been relatively few reports up till the last 20 years. In 2000, Benvenga et al. published one of the leading studies that drew attention and triggered more investigation on the issue. They had reviewed the literature and reported that pituitary dysfunction (PD) can develop years after the trauma, and may, on the contrary, improve with time. They also reported the young population was most frequently affected (6). The number of studies reporting PD increased significantly since then and it has now been established that even mild TBIs may cause PD with an onset years later (7).

PD may present with an acute life-threatening clinical picture but may also have subtle and nonspecific symptoms in the long term following an incident of trauma. For these reasons, predictive factors have been investigated and screening algorithms have been developed for PD in TBI patients.

We aimed to review the recent literature related to epidemiology, screening modalities, diagnosis, clinical presentations and therapy of PD following TBI. Relevant articles on PubMed published since 2000 were searched, as we stated before, from this time on the published literature has grown rapidly.

Clinical and Research Consequences

Pituitary dysfunction

Tanriverdi et al. reported the pooled prevalence rate of any pituitary hormone deficiency post-TBI as 28% and the rate of multiple hormone deficiencies as 6% in their systematic review. However, they pointed to the fact that included studies were heterogeneous in terms of TBI severity, the methods used to define the severity, the diagnostic procedures, and implementation of the confirmatory testing (7). In another recent review, the incidence of anterior hypopituitarism has been reported to occur from 5% to 76.4% (8). The reason for this wide range was due to these same factors.

In the review by Tanriverdi et al., the growth hormone (GH) deficiency was reported as the most common hormone dysfunction post-TBI with a prevalence of 9%. The prevalence of central hypoadrenalism, central hypogonadism, and central hypothyroidism was 6%, 5%, and 1%, respectively (7). The GH deficiency and central hypogonadism have generally been reported to be the most common across various studies, a fact explained by the vascular vulnerability of the anatomic area in which the somatotrophs and gonadotrophs are localized (7, 8).

As the awareness about PD has increased post-TBI, there has been an increasing concern about two specific groups, soldiers and athletes, who face the risk of the last two causes of TBI listed in Table 1. In a recent study, it was reported that 31% of veterans who at least had one blast-related mild TBI developed PD, while the rate was 15% among the control group. It was stated that the symptoms of PD overlapped significantly with those of posttraumatic stress disorder (PTSD) (9). The rate of PD due to sports-related TBIs was reported to range from 15% to 46.6% (10). The most common hormonal dysfunction was GH deficiency in both groups (9, 10).

Pathophysiology

Post-mortem studies of patients with fatal TBI revealed stalk rupture, hypothalamic and/or pituitary hemorrhage, or infarction (11). Shearing of small vessels during trauma may cause hypothalamic ischemic lesions and microhemorrhages. Venous engorgement caused by increase in intracranial pressure may also cause hypothalamic hemorrhage (12). Ventricular compression, intraventricular hemorrhage, and midline shift were associated with these lesions in the hypothalamus or pituitary. The long hypophyseal vessels that supply pituitary are vulnerable to trauma and the impaired circulation of these vessels may lead to gland infarction (7). Besides these "primary insults" that occur directly as a result of the trauma, a chain of subsequent pathophysiological events that cause hypotension, hypoxia, posttraumatic vasospasm, cerebral ischemia, brain edema, and increased intracranial pressure may also cause PD (7). These "secondary insults" are preventable with appropriate therapy.

Gonadotropic and thyrotropic dysfunctions and increased cortisol levels may be observed during the acute phase following trauma. These hormonal disturbances that improve during the follow-up mostly occur as a result of adaptive pathophysiological responses during critical illness (13). On the other hand, acute hormonal disturbances resulting from hypothalamo-pituitary damage may be reversible as well. Regeneration of portal vasculature and proliferation of remaining surviving cells may provide improvement in the functions of anterior pituitary (14). PD may develop even years after head trauma and one hypothesis based on pathological findings has been that the gradual scarring of the hypothalamus may be the cause of this phenomenon (15).

Table 1. The main causes of traumatic brain injuries

Traffic accidents
Falls
Assaults
War injuries
a. Blast-related injuries
b. Vehicular injuries
c. Falls
d. Bullet and fragment injuries
Sports-related injuries
a. Sports-related acute injuries
b. Chronic repetitive head trauma

PD that develops during the chronic phase has been associated with autoimmune mechanisms. Anti-pituitary (APA) and antihypothalamic antibodies (AHA) were detected in patients with autoimmune hypophysitis (16). Tanriverdi et al. reported the association with APA and AHA positivity and the development of PD in trauma patients. They analyzed boxers who had repetitive head trauma and confirmed the association between AHA positivity and hypopituitarism (17). Yet, there is a need for more studies to elucidate the underlying mechanism of autoimmunity leading to PD.

Many recent studies have pointed to the association between variable outcomes post-TBI and genetic polymorphisms of several cytokines, enzymes, and proteins that may be involved in the pathophysiologic process of TBI (18). However, there are very few studies that investigated the association between the genetic polymorphisms and the development of neuroendocrine dysfunctions following TBI. For the first time, Tanriverdi et al. reported lower rates of PD in TBI patients with an APOE3/E3 genotype of the apolipoproteinE (apoE), a lipoprotein that mediates the inflammatory processes in the brain. The rate of PD was 17.7% in patients with APOE3/E3 genotype and 41.9% in those without (OR=0.29, 95% CI=0.11–0.78, p=0.01) (19). Further studies are needed to investigate the genetic background of developing PD following TBI.

Follow-up of TBI Patients in Terms of Pituitary Dysfunction

Review of the risk factors

After TBI was been proven to be a cause of PD, development of evidence-based screening algorithms became an urgent necessity. The patients that required routine screening for PD were determined using predictive risk factors that had already been reported in the literature. However, there are conflicting results between studies and there is need for more investigations to define the precise risk factors.

Screening algorithms are usually based on the severity of trauma, as it is one of the strongest predictors for PD. The severity of TBI is universally assessed by the Glasgow Coma Scale (GCS) and is

Table 2. Scoring of the Glasgow Coma Scale

	Score
Eye opening	
Spontaneous	4
Response to verbal stimulus	3
Response to painful stimulus	2
No eye opening	1
Best verbal response	
Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
No verbal response	1
Best motor response	
Obeys commands	6
Localizing pain	5
Withdrawal from pain	4
Flexion to pain	3
Extension to pain	2
No motor response	1
Severity assessment	
Mild	3–8
Moderate	9–12
Severe	13–15

classified as mild, moderate, and severe based on the score obtained from the eye-opening status and the verbal and motor responsiveness to stimuli (Table 2) (20). One study reported that 42% of patients with a GCS score consistent with moderate or severe TBI had developed chronic PD (21). They also observed that diffuse brain swelling and hypotensive or hypoxic insults were associated with PD (21). On the other hand, Schneider et al. reported that initial GCS was not associated with hypopituitarism but that patients with secondary hypogonadism had a worse clinical status based on the modified Rankin scale score. They explained that the patients who developed brain edema or bleeding during follow-up had a worse clinical status than what was measured by the initial GCS score. They concluded that the severity should be evaluated in more detail with further studies (22).

Patients with GCS of mild TBI constitute a heterogeneous group in terms of symptomatology and outcome. The American Congress of Rehabilitation Medicine stated that for the diagnosis of mild TBI, at least one of the following criteria should be present: a) loss of consciousness of 30 minutes or less; b) a GCS score of 13–15 at 30 minutes after the trauma; c) loss of memory for events immediately before or not longer than 24 hours after the trauma; d) any alteration in the mental state (confusion, disorientation) at the time of the accident; and e) transient or permanent focal neurological deficits (23). However, this definition still comprises clinical heterogeneity. Mild TBI patients with depressed skull fractures or intracranial lesions on radiologic imaging have been sub-classified as "complicated mild TBI" by some authors, and this group was reported to have a worse outcome in terms of neurobehavioral functioning (24). Tanriverdi et al. reviewed the literature and reported that mild TBI patients developed PD more frequently in the presence of one of these features: a) radiological findings on initial CT or MRI, b) central adrenal insufficiency and/or central diabetes insipidus (DI) during acute phase, c) hospitalization for more than 24 hours, d) intensive care unit monitoring and/or any neurosurgical intervention, and e) APA and AHA positivity. They did not suggest routine screening of mild TBI patients who do not belong to the "complicated mild TBI" group (7).

Acute phase hormone deficiencies have been studied as predictors for long term PD. Pituitary function is highly dynamic post-TBI and hormonal disturbances occurring due to critical illnesses tend to improve during follow-up. Early-phase central cortisol deficiency and central DI were reported to be predictive of mortality as well as chronic PD (25).

Diffuse axonal injury, increased intracranial pressure, abnormal pupillary reactivity, presence of hypotensive or hypoxic insults, duration of coma, and duration of stay in the intensive care unit have been reported to increase the risk of PD. The association of PD with patient demographics such as age, gender, and BMI has been investigated too. However, none of these factors have been confirmed by all the studies in a consensus. Radiological findings such as diffuse brain swelling, intracerebral hematoma, multiple contusions, and skull base fractures during the acute phase and empty sella during the chronic phase were also associated with hormonal disturbances. However, it must be kept in mind that patients with hormonal deficiencies may have completely normal radiological findings (7, 26).

AHA and APA positivity were associated with PD as mentioned above and Tanriverdi et al. used AHA and APA positivity as one of the criteria to define "complicated mild TBI" (7). However, the authors stated that further studies are needed to verify the results (27). To our knowledge, there have been no other attempts in the literature to investigate a predictive biomarker for PD in trauma patients.

Screening Algorithms Proposed in the Literature

One of the first articles suggesting a screening modality for PD in TBI patients was published in 2000 (6). Lacking prospective studies at the time, Benvenga et al. proposed the "3/4" rule as a screening strategy. They stated that about 3/4th of TBI patients with PD were males of age ≤40 years, 3/4th of these cases were due to road accidents, and that PD develops during the first year in 3/4th of cases. They offered follow-up for patients that met these criteria (6). Schneider et al. suggested the evaluation of PD in all TBI patients regardless of the severity in their study and they reported no association between GCS and hormonal dysfunction (22).

In 2005, Ghigo et al. published the first consensus guideline on the issue (26). They recommended that patients in a permanent vegetative state or who function at a very low level and are institutionalized should only be assessed for DI, inappropriate ADH syndrome, and cortisol and thyroid hormone deficiencies because these patients are not expected to benefit from GH or gonadal hormone replacement. Excluding this group, the authors recommended the assessment of all moderate and severe TBI patients with baseline hormonal testing. They suggested prospective screening for PD

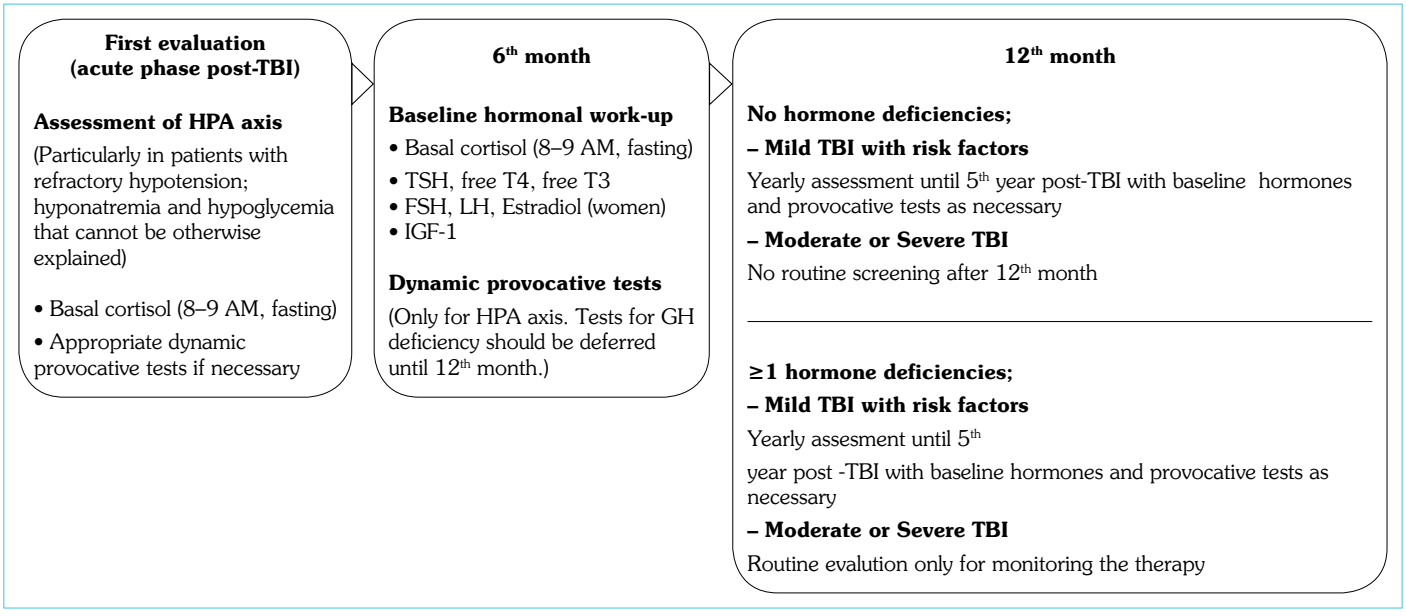

Figure 1. Prospective screening algorithm of pituitary dysfunction post-TBI

with baseline hormonal evaluation in all TBI patients at 3rd and 12th months following TBI. Retrospective screening of PD was recommended for moderate and severe TBI patients who complained of symptoms consistent with hypopituitarism at 12 months after the trauma (26).

Tanriverdi et al. suggested a screening algorithm that also included patients with mild TBI. As stated above, they defined the risk factors of PD in mild TBI patients and narrowed down the number of those who should be screened. Also, similar to Ghigo et al., they excluded severely disabled and vegetative patients too. Patients who were monitored in ICU or were hospitalized for more than 24 hours, regardless of the severity of TBI, were recommended for testing during the acute phase and were screened for PD prospectively. Screening for hormonal insufficiencies was also recommended for complicated mild TBI, moderate TBI, and severe TBI patients. The American Association of Clinical Endocrinologists (AACE) recommended testing for PD in moderate and severe TBI patients and symptomatic and mild TBI patients (28). The British Neurotrauma Group (BNG) suggested evaluation for PD in patients who were hospitalized for more than 48 hours or in those with signs or symptoms suggestive of PD (29).

Baseline cortisol measurement was the only test suggested to be performed during the acute phase in the algorithm developed by Tanriverdi et al. (7). Recommendations on hormonal evaluation during the acute phase were limited to the hypothalamo-pituitary adrenal axis and the posterior pituitary by the AACE as well (28). However, BNG did not suggest any routine testing and recommended that in cases of suspicion of adrenal insufficiency, therapy must be started immediately (29).

In the guidelines published by Ghigo et al. and AACE, the duration of screening was limited to 12 months with an explanation that there is no evidence for longer a follow-up (28). The BNG suggested testing at 3–6 months (29). A group of experts published a manifesto for the management of TBI-induced PD in 2011 and suggested screening up to 3 years post-TBI (30). Four years later, Tanriverdi et al. recommended testing up to 5 years, the rationale being mainly based on the results of 3 prospective studies. They stated that pituitary hormonal changes in terms of improvement or worsening were observed during 5 years after TBI. These dynamic changes were more likely to occur in complicated mild TBI patients, and for this reason, they recommended yearly re-assessments for this group, while only monitoring the titration of the replacement therapy was suggested for moderate and severe TBI patients (7). The screening algorithms are summarized in Figure 1 (7, 30).

Clinical Perspectives and Diagnosis of Anterior Pituitary Dysfunction Post-TBI

Patients with GH deficiency may have a low energy status, cognitive impairment, decreased muscle mass and exercise capacity and increased cardiovascular morbidity as a result of hypertension, increased intima-media thickness, dyslipidemia, and abdominal adiposity (7, 31, 32). GH deficiency is reported as one of the most frequent hormonal disturbances following TBI and the young population with long life expectancy constitutes the majority of TBI patients (7). In light of these data, the possible detrimental effects of GH deficiency over the health of the population and its burden on health care can be better understood.

Deficiency in GH was reported to be highly reversible during the first year after TBI and there has been no evidence of benefit from replacement during the early phase. For these reasons, the evaluation of GH deficiency was generally recommended to be deferred until 12 months post-TBI (7, 26). Moreover, only patients with intention to treat are recommended to be tested for GH deficiency. Baseline IGF-1 measurement constitutes first-line testing. A low IGF-1 level is suggestive of GH deficiency but clinicians should be aware of other factors that may cause IGF-1 levels to be below the reference range, such as oral estrogen replacement or uncontrolled diabetes mellitus. On the other hand, IGF-1 levels in the normal range would not exclude the diagnosis and stimulation tests would be required in most cases. It is of utmost importance that hypocortisolemia and thyroid hormone insufficiencies be treated appro-

Table 3. Diagnostic tests for anterior pituitary dysfunction

	Baseline hormonal evaluation	Stimulatory tests	Comments
Central hypoadrenalism	Serum cortisol level (8–9 AM, fasting) Indicative of insufficiency: <3 µg/dL Indicative of sufficiency: >15 µg/dL	GST Indicative of sufficiency: peak cortisol level >18 µg/dL (Local cutoff: >10.74 µg/dL (34) ITT Indicative of sufficiency: peak cortisol level >18.1 µg/dL Corticotropin stimulation test (250 mcg or 1 mcg) Indicative of sufficiency: peak cortisol level >18.1 µg/dL (Local cutoff for 1 mcg ACTH: >12.5 µg/dL)	– May not be appropriate for some TBI patients Should be performed at least 3 months after TBI
Growth hormone deficiency	IGF-1 (Use age-adjusted reference ranges)	GHRH+Arginine test Indicative of insufficiency: Indicative of sufficiency: peak GH level Indicative of sufficiency:	May not be diagnostic for hypothalamic insults –
Central hypogonadism	Total testosterone (men) Estradiol (women) Low sex steroids with low/normal gonadotropin levels	–	Measurement during acute phase may be misleading
Central hypothyroidism	levels fT4 below reference range with low/normal/elevated TSH	–	Measurement during acute phase may be misleading

FSH: Follicle stimulating hormone; GHRH: Growth hormone releasing hormone; GST: Glucagon stimulation test; IGF-1: Insulin like growth factor-1; ITT: Insulin tolerance test; LH: Luteinizing hormone; TSH: Thyroid-stimulating hormone

priately before testing, as the results in the alternative case may be misleading. Stimulation tests and diagnostic cutoff values are presented in Table 3. The diagnosis of GH deficiency is established when three or more pituitary hormone deficiencies are present with a low IGF-1 level and confirmation with a stimulatory test is not required in this case. However, for the diagnosis of isolated GH deficiency, two provocative tests are said to be insufficient (32).

Adrenal insufficiency must be considered in TBI patients with hyponatremia, hypotension, or high requirements of vasopressors during the early phase after the trauma (28). Baseline cortisol measurement is suggested during the acute phase post-TBI by most authors as explained in the "screening" section above. Stimulation tests are recommended in cases when early morning cortisol levels are in the range of 3µg/dL to 18µg/dL. Insulin tolerance test is the gold standard test to measure cortisol levels. However, it may be dangerous in some TBI patients and should be avoided. The Synacthen test may be misleading if performed during the early phase post-TBI. Various diagnostic cutoff values of stimulatory tests are used by different clinics. The universally most commonly used values (33) as well as the local values (34, 35) used by the Endocrinology Clinic at Erciyes University are presented in Table 3. Clinicians must be aware of the possibility of insidious onset of adrenal insufficiency during the long-term follow-up and patients may present with nonspecific complaints such as dizziness, tiredness, anorexia, and weight loss (28). In cases of suspicion, appropriate diagnostic tests and therapy should be performed without delay.

Patients who develop central hypothyroidism following TBI may present with classical signs and symptoms of primary hypothyroidism such as fatigue, depression, cognitive disturbances, cold intolerance, dryness of skin, constipation, and bradycardia. These symptoms generally manifest in a milder form (36). The diagnosis of central hypothyroidism and central hypogonadism is mainly based on the evaluation of baseline hormone levels. Monitoring of these hormones during acute phase post-TBI and critical illnesses may be misleading due to the functional suppression of the stress response. On the other hand, the long half-life of free thyroxine

(fT4) may mask the underlying thyrotrope dysfunction, due to which an evaluation at 4–6 weeks post-TBI is recommended (28). Detection of low fT4 levels with inappropriately low or normal TSH levels indicates the diagnosis of TBI. High TSH levels may be detected in some cases of central hypothyroidism due to biologically inactive TSH (36).

The clinical picture of hypogonadism depends on the age of onset in both men and women. Pre-pubertal onset may cause eunuchoidism and disturbances in sexual maturation with other signs and symptoms that may be observed in the post-pubertal onset, such as loss of libido, infertility, and low bone mineral density (37). Gynecomastia, erectile dysfunction, loss of facial and body hair, decrease in muscle mass, and strength are other indicators of hypogonadism in men (37). Low levels of serum testosterone during early morning fasting and low FSH and LH levels confirm the diagnosis of central hypogonadism. Pre-menopausal adult women with a history of TBI may develop menstrual irregularities, amenorrhea, and infertility. The diagnosis is confirmed with low estradiol and low FSH and LH levels. Post-menopausal women will not have any complaints regarding central hypogonadism and gonadotroph dysfunction is diagnosed with low FSH and LH levels that are inconsistent with menopause.

Treatment of Anterior Pituitary Dysfunction Post-TBI

As mentioned above, patients in the vegetative state or those with low life expectancy should be treated for hypocortisolemia, thyroid hormone insufficiency, and posterior PDs, but these patients are not considered suitable for the replacement of GH or gonadal insufficiencies (26). Young patients constitute the majority of TBI survivors and are usually candidates for replacement therapies.

GH replacement has been reported to improve cognitive functions and quality of life in TBI patients (7, 31). In terms of cardiovascular risk factors, a significant number of studies reported a decrease in blood pressure and intima-media thickness, improvement in endothelial function, decrease in LDL cholesterol, and increase in HDL cholesterol levels. However, more inconsistent results have been reported related to glucose metabolism (31, 32). Increase in the lean body mass and reduction in fat mass were reported by most authors, both of which also had favorable effects on bone mineral density (31, 32, 38). Growth hormone replacement modality in TBI patients does not differ from other adult-onset GH deficient patients (32).

Levothyroxine replacement is recommended to be started at lower doses and titrated accordingly to target the upper half of the reference range for free T4 levels. Serum TSH levels are not useful for monitoring the therapy (36). Hypocortisolemia should be excluded or appropriately treated before the restoration of the thyroid hormone. Oral hydrocortisone, usually administered at 15–20 mg daily in divided doses, is generally suggested for the treatment of adrenal deficiency in ambulatory patients and parenteral replacement is recommended for adrenal crisis or perioperative management (33).

Androgen replacement will restore anemia, lean body mass, muscular strength, libido, erectile dysfunction, and a sense of well-being in men (37). Treatment of hypogonadism will improve bone mineral density in both sexes. The clinician will decide on the strategy of replacement therapy depending on the age, fertility desire, concomitant diseases, and risk factors of the patient.

Central Diabetes Insipidus: Dysfunction of Posterior Pituitary Following TBI

Agha et al. reported the occurrence of central DI as 21.6% during the acute phase post-TBI with permanence in 6.9% of these patients (39). They observed that the development of central DI was associated with the severity of the trauma. Damage to the stalk or posterior pituitary may lead to the development of central DI (28). Urine volume exceeding 50 mL/kg every 24 hours with serum osmolarity of >295 mOsm/L and an inappropriately low urine osmolarity are all suggestive of the diagnosis (33). Not all cases can be diagnosed by baseline analysis, and the water deprivation test can be performed for confirmation of TBI. Desmopressin therapy should be individualized and the possibility of recovery should be kept in mind (33).

CONCLUSION

PD is a common complication of TBI, which may develop even years after mild and forgotten head injuries. Signs and symptoms of PD may be nonspecific and complaints such as cognitive impairment, psychiatric problems, and decreased quality of life may be attributed to TBI itself. The onset of hormonal dysfunctions may be insidious and awareness is required to suspect the diagnosis. Moreover, as cortisol and thyroid hormones are of vital importance, undetected PD may have life-threatening consequences. For these reasons, screening algorithms have emerged during recent years. Various risk factors have been proposed and novel investigations about the genetic polymorphism and autoimmunity paved the way for further studies. The data so far is conclusive enough to warn clinicians to be attentive to hormonal disturbances in TBI patients, but further studies are needed to provide insights on the complicated underlying mechanisms, risk factors, and biomarkers for screening purposes.

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