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Traumatic Brain-Injury-Induced Hypopituitarism: Clinical Management and New Perspectives

ABSTRACT

Once being a neglected etiologic factor, traumatic brain injury is now acknowledged as an important risk factor for pituitary dysfunction. The gland might be damaged as a result of primary or secondary injury. The prevalence of pituitary dysfunction is highly variable across studies. The occurrence rate during acute and/or chronic phases was reported up to 69% in some series, while the rate of persistent hypopituitarism decreased to 12% when confirmatory testing was conducted. Growth hormone deficiency emerges as the most prevalent hormone deficiency subsequent to traumatic brain injury, followed by adrenocorticotropic hormone, gonadotropins (follicle-stimulating hormone and luteinizing hormone), and thyroid-stimulating hormone deficiencies. Pituitary function tends to be dynamic following traumatic brain injury; hormone insufficiencies may improve, and new deficiencies may occur during follow-up. The clinical findings of pituitary hormone deficiencies may vary widely from non-specific and subtle symptoms to urgent life-threatening conditions such as hypotension and hyponatremia. Timely diagnosis is of utmost importance, and it requires awareness and a high level of suspicion. Screening algorithms have been developed to guide clinicians on who should be tested for pituitary dysfunction, how, and for how long following traumatic brain injury. However, the rate of routine screening is still low among clinicians. We aimed to review the current literature focusing on the diagnosis and clinical management of pituitary dysfunction following traumatic brain injury.

Keywords: Traumatic brain injury, hypopituitarism, pituitary, growth hormone deficiency, head trauma

Introduction

Traumatic brain injury (TBI) is the impairment of the brain structure and/or function caused by an external force.[1] The external force might be generated by various mechanisms such as a penetrating or dull object striking the head, the head striking against an object, whiplash, or blast injuries.[1] A meta-analysis published in 2018 reported an estimated worldwide incidence of TBI as 69 million each year.[2] The incidence was higher in low- and middle-income countries, and the leading causes of TBI vary across countries.[2] Males are more frequently affected than females, and adolescents and adults are affected more than children and elderly.[2]

Traumatic brain injury may cause permanent disabilities and neuroendocrine impairments are now well-recognized potential sequelae.[3] A recent meta-analysis reported that one-third of TBI patients had pituitary dysfunction 1 year after the trauma.[3] It may occur not only after moderate-to-severe TBI but also following mild TBI.[3] Clinical findings depend on the underlying hormone deficiency and may vary greatly. Pituitary dysfunction may present with urgent symptoms such as hyponatremia, hypoglycemia, hypotension, and hypotensive crisis, while fatigue, decreased energy level, nausea, loss of muscle mass and increase in fat mass, hypogonadism symptoms, and decreased quality of life (QoL) are among the non-specific chronic symptoms.[4]

Timely diagnosis of pituitary dysfunction is of utmost importance both during acute and chronic phases to prevent life-threatening consequences and to increase the general well-being of the patient. Therefore, different study groups developed screening algorithms for pituitary dysfunction following TBI.[4-7] However, there are inconsistencies in the literature regarding who should be screened, at what intervals, and for how long. Traumatic brain injuries generate a heterogeneous patient population in terms of clinical presentation, hence the risk of development of pituitary dysfunction also varies greatly.[8] Many authors investigated the risk factors for the development of pituitary dysfunction following TBI, but the results are inconsistent.[9] Moreover, pituitary hormones are highly dynamic following TBI, further complicating the process of generating screening recommendations.[8] On the other hand,

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a recent study showed that the rate of screening for pituitary dysfunction following TBI is low among clinicians and that the indications for screening varied widely.[10]

We aimed to review the current literature, focusing on the screening algorithms, diagnostic modalities, and treatment strategies for pituitary dysfunction following TBI. A clinical perspective of view was followed in the text with an intention to make a contribution to increased use of literature recommendations during bedside practice.

Rationale for Evaluation of Pituitary Dysfunction Following Traumatic Brain Injury

The prevalence of long-term pituitary dysfunction after TBI ranges from 6.3% to 69.5% across prospective studies.[9] The main causes of this wide range are the different patient populations with various severities of TBI tested with different diagnostic tests and cut-off values.[11] However, when confirmatory testing is conducted, the prevalence of persistent hypopituitarism decreases to approximately 12%.[4] Growth hormone (GH) deficiency emerges as the most prevalent hormone deficiency subsequent to TBI, followed by adrenocorticotropic hormone (ACTH), gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and thyroid-stimulating hormone (TSH) deficiencies.[3,4] The high prevalence of GH deficiency is explained by the peripheral localization of somatotrophs and vulnerable vascular supply.[12] As TBI may cause pituitary dysfunction immediately following trauma or months and even years later,[8] the evaluation time may also affect the rate. Considering the high occurrence rate of TBI in the population, the development of neuroendocrine dysfunction emerged as an alarming risk for public health.

Pituitary damage following TBI may occur through either primary or secondary injuries.[4,12] Direct mechanical injuries during head trauma are classified as "primary," and indirect injuries due to subsequent events after trauma such as hypotension, ischemia, edema, etc., as "secondary."[13] Regenerative neural as well as vascular mechanisms may be protective from permanent hormone deficiencies, while triggering of fibrosis may cause life-long pituitary dysfunction.[12,14] Pathophysiologic mechanisms of pituitary dysfunction following TBI are reviewed elsewhere.[4,12]

The acute phase is defined as the first 14 days after TBI, and the chronic phase as >3 months after TBI.[4,12] Pituitary functions are highly dynamic following TBI, and hormone deficiencies during the acute phase may improve during follow-up, while new deficiencies may develop during long term.[8] The analysis of the data from the German database indicated that the prevalence of GH deficiency increased with time and central adrenal insufficiency decreased.[15]

Considering the high prevalence of TBIs and hence the high risk of pituitary dysfunction, persistent risk of developing new hormone deficiencies during follow-up and potentially serious clinical implications on patient's life justify routine screening of pituitary dysfunction following TBI.

Risk Factors and Proposed Markers for Pituitary Dysfunction Following Traumatic Brain Injury

One of the main questions regarding the evaluation of post-TBI pituitary dysfunction is who to screen during acute and chronic phases. The majority of TBI cases consist of mild TBIs in which the risk for pituitary dysfunction is not high enough to justify routine screening in all mild TBI patients.[4] On the other hand, patients with severe TBI who are severely disabled and institutionalized would mainly need the replacement of vital hormones such as glucocorticoids.[4] For these reasons, a need for specific predictive factors emerged and a growing literature is reporting on probable factors. However, there are inconsistencies between studies.

The severity of TBI is one of the most commonly investigated predictive factors across studies. Glasgow coma scale (GCS) score is generally used to define the severity of the trauma, where the scoring is based on eye opening, verbal, and motor response.[16] Glasgow coma scale score was negatively correlated with the rate of pituitary dysfunction following trauma,[17] but not all studies reported an association.[18] On the other hand, there are limitations of GCS scores when determining screening groups for pituitary dysfunction. The severity groups determined according to GCS are heterogeneous in themselves. Some factors related to TBI severity such as temporary loss of consciousness, presence of amnesia, or radiologic findings are not included in the GCS score while they are associated with pituitary dysfunction.[19] For this reason, screening algorithms have been based on some other factors such as alteration of consciousness, length of hospital stay, ICU monitoring, neurosurgical intervention, etc., besides GCS score.[4,6,17]

Some early clinical parameters were associated with the development of pituitary dysfunction following TBI. Silva et al[19] reported an increased risk of pituitary dysfunction in patients who had motor vehicle accidents, post-traumatic seizures, focal cortical contusions, and intracranial hemorrhages. Diffuse axonal injury, older age, and surgical intervention were reported as risk factors in other studies.[20] The rate of hypopituitarism was also correlated with the length of total hospital stay, ICU stay, and intracranial hypertension.[17] Diffuse brain swelling and hypotensive and hypoxic insults were other risk factors.[21] The development of hypocortisolemia and central diabetes insipidus (DI) during the acute phase following TBI was associated with pituitary dysfunction during the long term.[22] In another study, high cortisol and low GH levels were associated with long-term GH deficiency.[23]

The genetic polymorphisms of some mediators, their receptors, and enzymes may affect repair mechanisms and were associated with recovery rates and outcomes after TBI.[24] However, the association between polymorphisms and neuroendocrine function following TBI is not investigated in depth. Tanriverdi et al [25] showed the association between apolipoprotein E (APO E) polymorphism and the development of pituitary dysfunction following TBI. Patients with APO E3/E3 polymorphism had a decreased rate of pituitary dysfunction in this preliminary study.[25] Considering these evidences, polymorphisms of certain genes might be risk factors for permanent neuroendocrine dysfunctions following TBI. However, there is a need for further studies.

Taheri et al[26] investigated the association between microRNA profiles and pituitary dysfunction of TBI patients during acute and chronic phases for the first time. The authors reported that serum levels of microRNA-126-3p and microRNA-3610 were associated with pituitary dysfunction following TBI, and they proposed the use of microRNAs as predictive markers for pituitary dysfunction.[26] Anti-pituitary antibodies (APA) and anti-hypothalamic antibodies (AHA) were investigated as players in pathogenesis and potential markers previously.[27-29] Tanriverdi et al[28] reported an association between the presence of APA and AHA positivity and long-term pituitary dysfunction. The positivity of these antibodies was also included as a risk factor in the screening algorithm developed by the authors[4] (Figure 1).

Screening not suggested;

- Vegetative state
- Low life expectancy
- Mild TBI:
  - No loss of consciousness
  - Post-traumatic amnesia <30 min

Screening suggested;	Evaluation during acute-phase	Evaluation during chronic-phase	
	Hormonal evaluation for; - Central adrenal insufficiency Measurement of baseline cortisol[1]; (diagnostic cut-off: ≤11 µg/dL) [1] On day 1-4 after injury measure cortisol in every patient, on 5-10 after injury cortisol measurement in case of clinical suspicion (hyponatremia, hypotension, hypoglycemia)	**6th month** Hormonal evaluation for; - Central adrenal insufficiency - Central hypothyroidism - Central hypogonadism	**12th month** Hormonal evaluation for; • Central adrenal insufficiency • Central hypothyroidism • Central hypogonadism • GH deficiency
• Need for hospitalization for ≥24 hours • Need for ICU monitoring	+	+	Yearly follow-up until 5 years
• Complicated mild TBI: • Presence of radiologic changes on CT/MR during admission • Central adrenal insufficiency and/or central diabetes insipidus during acute phase • Hospitalization for ≥24 hours • ICU monitoring • Neurosurgical intervention • Being positive for anti-pituitary antibody, anti-hypothalamic antibody	+	+	Yearly follow-up until 5 years *(pituitary deficiencies may recover or rarely new-onset deficiencies may develop)*
• Moderate TBI • According to GCS	+	+	Stop screening in case of no hormone deficiencies at 12th month
• Severe TBI: • According to GCS • Presence of loss of consciousness and/or confusion > 30 min • Presence of post-traumatic amnesia >24 h	+	+	*(the patients should be reminded regarding the symptoms of hypopituitrism and could be re-evaluated if symptomatic)*

Figure 1. Recommendations for evaluation of pituitary dysfunction during acute and chronic phases following TBI *(Derived from references 4, 51)*. TBI, traumatic brain injury.

None of the radiologic findings reported so far were predictive enough for pituitary dysfunction, though some studies reported associations. Basal skull fractures, brain swelling, and the presence of subdural hematoma are among those associated with pituitary dysfunction.[20,30] One study reported a significantly increased volume of the pituitary gland during the acute phase following TBI that normalized during follow-up.[31] However data regarding gland function were missing.[31] Decrease in gland volume and empty sella were observed during the chronic phase and were associated with hormone deficiencies.[32,33]

Clinical Findings and Diagnostic Modalities of Pituitary Dysfunction Following Traumatic Brain Injury

Central Adrenal Insufficiency

It is of utmost importance for clinicians to be aware of the risk of central adrenal insufficiency in TBI patients both during the acute and chronic phases. Hypotension resistant to vasopressors, hyponatremia, and hypoglycemia are among the alarming signs during the acute phase (Table 1). The diagnosis is based on the measurement of baseline serum cortisol level. A 09:00 AM serum level of ≤11 µg/dL, which was derived from the data of critically ill patients, was reported to be suggestive of the diagnosis during the acute phase in TBI patients.[22] In cases when serum cortisol measurements will be time-consuming or cannot be performed, but a clinical suspicion of adrenal insufficiency exists, glucocorticoid replacement should be started straightforwardly without waiting for the test results to avoid potentially life-threatening consequences.

The use of stimulation tests is not routinely recommended during the acute phase.[4,22] The adrenal glands will still be responsive to synacthen stimulation until 4-6 weeks after acute pituitary damage.[22] Insulin tolerance test (ITT) may not be safe in patients with acute head trauma, and the glucagon stimulation test (GST) might be misleading.[22] A patient with TBI may also have multiple injuries that might become complicated with sepsis and septic shock during the hospital stay. Relevant guidelines for critical illness-related corticosteroid insufficiency (CIRCI) should be followed in these patients.[34]

The clinical findings of adrenal insufficiency during the chronic phase might be non-specific and subtle (Table 1), and the diagnosis might require a high grade of suspicion. The diagnostic process in TBI patients during the chronic phase is not different from other etiologies, and relevant guidelines are to be followed.[35] A baseline serum cortisol level less than 3 µg/dL is suggestive of the diagnosis, and a level higher than 15 µg/dL excludes the diagnosis.[7,35,36] For the values in between the stimulation tests should be performed.[35] Table 1 presents various diagnostic cutoff values used for adrenal insufficiency and GH deficiency. Karaca et al[37] showed that a cutoff of 12.5 µg/dL during low-dose synachten stimulation test (1 µg), and a cutoff of 9.1 µg/dL during GST can accurately diagnose adrenal insufficiency. Berg et al[38] reported a cutoff value of 10 µg/dL during GST. The guidance for pituitary insufficiency by the Society of Endocrinology and Metabolism of Turkey (SEMT) suggests the use of a cutoff of 9-10 µg/dL for adrenal insufficiency during GST.[36]

Central Hypothyroidism

The half-life of free T4 is 7 days, and the routine evaluation of the thyroid axis is not necessary during the acute phase.[4] Moreover, caution should be practiced during the evaluation of thyroid function tests in critically ill patients with TBI. A critically ill state may not only cause inhibition of deiodinase and lead to low T3 levels but also low free T4 levels in severe cases.[39]

Patients may present with symptoms of hypothyroidism during the chronic phase (Table 1). Low serum free thyroxine (T4) levels with a low, normal, or mildly elevated serum TSH level are suggestive of

Table 1. Clinical Features of and Diagnostic Tests for Pituitary Dysfunction

Hormone Deficiency	Signs and Symptoms	Diagnostic Tests
Central adrenal insufficiency	Fatigue, dizziness, nausea, vomiting, anorexia, weight loss, pallor Hypotension, shock, hyponatremia, hypoglycemia, anemia, lymphocytosis, eosinophilia	**Baseline evaluation** Serum cortisol level (fasting, 8-9 AM) Insufficient response: Cortisol level: <3 μg/dL (adrenal insufficiency) 3-15 μg/dL (verification required with stimulation tests) **Stimulation tests** **Corticotropin stimulation test** ***Synachten 250 μg:*** Insufficient response: Peak cortisol level: <18 μg/dL ***Synachten 1 μg:*** Insufficient response: Peak cortisol level: <18 μg/dL, : <12.5 μg/dL* **Insulin tolerance test** Insufficient response: Peak cortisol level: <18 μg/dL **Glucagon stimulation test** Insufficient response: Peak cortisol level: <18 μg/dL : <9-10 μg/dL*
Central hypothyroidism	Fatigue, decline in cognition, cold intolerance, constipation, dry skin, loss of hair Hoarseness, weight gain, bradycardia, hypertension, hyponatremia	**Baseline evaluation** Serum free T4 Serum TSH **Stimulation tests** None
Central hypogonadism	Male: Fatigue, loss of muscle strength and mass, loss of body hair, erectile dysfunction, depression Female: Menstrual irregularities, atherosclerosis Both sexes: Loss of libido, infertility, osteoporosis	**Baseline evaluation** Male: Serum testosterone, FSH, LH (fasting, before 10 AM) Female: Estradiol, FSH, LH **Stimulation tests** None
Growth hormone deficiency	Fatigue, distortion of body composition (muscle mass↓, fat mass↑), cognitive impairment, decreased quality of life Insulin resistance, dyslipidemia, atherosclerosis	**Baseline evaluation** Serum IGF-1 level • Age and sex-adjusted reference**Stimulation tests** **Insulin tolerance test** Insufficient response: Peak GH level: <3 μg/L **Glucagon stimulation test** Insufficient response: Peak GH level: <3 μg/L or 1 μg/L (refer to text) : <1.1 μg/L* **GH-releasing hormone-Arginine test** Insufficient response: Peak GH level: ≤11.5 μg/L (BM I<25 kg/m^2) ≤8 μg/L (BMI 25-30 kg/m^2) ≤4.2 μg/L (BMI ≥30 kg/m^2) **Macimorelin test** Insufficient response: Peak GH level: ≤2.8 μg/L
Central diabetes insipidus	Polyuria, nocturia, polydipsia Hypernatremia, low urine osmolarity	**Baseline evaluation** Serum Na level, serum and urine osmolarity, copeptin level **Stimulation tests** Water restriction test

*The diagnostic cutoff values for adrenal insufficiency and GH deficiency are verified by national studies.[36]
FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor-1; LH, luteinizing hormone; T4, thyroxine; TSH, thyroid-stimulating hormone.

central hypothyroidism.[35] There are no stimulation tests to be routinely performed for the diagnosis.

Central Hypogonadism

Central hypogonadism might be suspected in male patients with low-serum total testosterone levels measured before 10 AM, with low or inappropriately normal serum LH and FSH levels.[35] The diagnosis in pre-menopausal female patients is based on menstrual irregularities such as oligomenorrhea or amenorrhea with low-serum estradiol levels, and low- or normal-serum LH and FSH levels.[35] Inappropriately low levels of LH and FSH in post-menopausal women will suggest the diagnosis. Other etiologic factors that might suppress the gonadal axis (e.g., high prolactin level and use of medications) should be excluded before definite diagnosis.[35]

Growth Hormone Deficiency

Growth hormone deficiency might have detrimental effects on the overall health in many aspects such as impairment in body composition, decline in cognitive functions, and decreased QoL (Table 1). Growth hormone deficiency should be evaluated in patients with TBI during the chronic phase, and the diagnosis is no different from other etiologies.[4] It is not necessary to screen patients who are not intended to be started on the GH replacement.

A single measurement of serum IGF-1 level may be misleading in TBI patients, and stimulation tests should be performed for the diagnosis.[40] In case of suspicion of isolated GH deficiency, the diagnosis should be verified by 2 stimulation tests.[41] If there is a dysfunction of 3 or more pituitary axes along with low IGF-1 levels, GH deficiency can be diagnosed.[41]

The gold standard stimulation test is ITT.[41] It is contraindicated in patients with certain comorbidities such as seizures, antiepileptic drug use after TBI, and coronary artery disease.[41] The alternative tests are GST, Growth Hormone Releasing Hormone (GHRH) + arginine, and the novel macimorelin test (Table 1). The generally accepted diagnostic cutoff value for GST is 3 μg/L.[41] However, Tanriverdi et al[42] suggested a cutoff of 1.18 μg/L in their study with TBI patients. Several years later, the same group reported a cutoff of 1.07 μg/L as more specific in the study that GST was compared to ITT verifying previous results.[43] Dichtel et al[44] proposed a diagnostic cutoff of 1 μg/L for GST but only for overweight/obese patients. This cutoff was further verified by a prospective randomized controlled study.[45] In 2019 guideline of the American Association of Clinical Endocrinologists (AACE), a cutoff of 3 μg/L was recommended for patients with BMI <30 kg/m^2 and a high pretest probability, while 1 μg/L for those with BMI >30 kg/m^2 and a low pretest probability.[46] The results of studies performed by our group and our clinical experience indicate a cutoff of 1.1 μg/L to be more accurate for GH deficiency during GST, decreasing the rate of false positivity. Therefore, it is routinely applied in our clinical practice and also recommended by guidance for pituitary insufficiency by SEMT.[36]

GHRH is not universally available, thus the test cannot be routinely performed. Macimorelin stimulation test is a novel test that proved efficient and safe for the diagnosis of GH deficiency but is expensive and not easily accessible yet.[47]

Diabetes Insipidus

Injury of the posterior pituitary or pituitary stalk following TBI may result in central DI. The prevalence widely ranges from 3% to 51%.[48] Permanent DI was reported to occur in 7% of the patients mostly being a partial insufficiency. The occurrence of DI was associated with the severity of TBI.[48]

Patients who develop polyuria following TBI should be suspected of central DI. The diagnosis might be confounded in patients followed in intensive care units by excessive volumes of fluids, diuretics, or hyperosmolar solutions. Polyuria is defined as urine volume >3500 mL/24 h.[49] The diagnosis of DI was established in cases of polyuria, high serum osmolarity (>300 mOsm/L), hypernatremia (>145 mmol/L), and urine not reaching an appropriate level of concentration (urine/plasma osmolality <2)[49] though different cutoff values have been proposed in the literature.[48] Water restriction test is the most commonly performed test for the diagnosis.[50] Measurement of plasma copeptin is also of diagnostic value but seldom used during clinical management.[50]

Screening and Follow-Up Strategies for Pituitary Dysfunction Following Traumatic Brain Injury

Indications for Screening

Screening strategies that were developed by different groups based their recommendations regarding who should be screened on various risk factors from the literature reviewed above. The severity of the TBI evaluated by GCS is the most commonly used tool for screening.

In the first consensus guidance published in 2005, it was recommended that all patients with TBI regardless of severity should be evaluated prospectively at third and twelfth months with baseline hormonal tests.[5] Also patients who had TBI at a time longer than 12 months ago and had symptoms suggestive of hypopituitarism were recommended to be tested.[5] However, including all patients with TBI in routine screening programs would neither be cost-effective nor necessary as the patients with mild TBI that do not have an increased risk of pituitary dysfunction will comprise the majority of TBI patients.[4] Therefore, the screening algorithms published in the following years proposed that mild TBI patients with additional risk factors should be screened (Figure 1).[4,51]

Tanriverdi et al[4] excluded patients with mild TBI who had no other risk factors from screening and defined the group "complicated mild TBI" based on risk factors from the literature. In the guidance developed by AACE loss or alteration of consciousness, post-traumatic amnesia was included in the classification system besides GCS.[7] The symptomatic patients who had low QoL and mild TBI and those who had moderate and severe TBI were recommended to be evaluated for pituitary dysfunction both during acute and chronic phases.[7] British Neurotrauma Group recommended that patients who were hospitalized longer than 48 h for TBI should be evaluated at 3-6 months post-TBI. The patients who were not hospitalized or hospitalized for shorter durations should be tested in case of any complaints consistent with pituitary dysfunction.[6]

Timing of Screening

Acute Phase

There is a consensus among screening algorithms developed by various groups that adrenal insufficiency and central DI are the only pituitary hormone deficiencies to be tested during the acute phase.[4,6,7] Acute trauma and critical illness may induce suppression of thyroid, GH, and gonadal axes, and the results might be indistinguishable from pituitary dysfunction during this phase.[39]

Some authors recommended testing only symptomatic patients for adrenal insufficiency.[6] However, in the algorithm developed

by Tanriverdi et al[4] routine screening was recommended for the patients with risk factors during the first 4 days after TBI and in case of suspicion until the tenth day (Figure 1).

Chronic Phase

Evaluation of central hypothyroidism, central hypogonadism, and GH deficiency is recommended to be deferred 3-6 months after TBI.[4,7,52] The reasons are (1) the adaptive responses of these pituitary axes are biochemically indistinguishable from pituitary dysfunction,[39] (2) the dynamic nature of pituitary hormones shortly after TBI and the possibility of spontaneous improvement, and (3) lack of evidence regarding clinical benefits and safety of replacement of GH and gonadal steroids shortly after TBI.

Prospective screening recommendations are generally based on the severity of TBI.[4,52] The severity of TBI was reported to affect the reversibility of pituitary hormones.[4] Patients who had mild TBI had a higher chance to regain the function of pituitary axes, while it was not the case in patients with severe TBI whose hormone deficiencies are generally persistent.[4] These patients should be followed for dose titration of replacement therapies rather than for an improvement possibility. That is the rationale behind the longitudinal screening algorithm developed by Tanriverdi et al.[4] Figure 1 depicts short- and long-term screening strategies suggested by our study group.[4]

The screening duration of 5 years has been based on the data from prospective studies, and further screening should be individualized. Krewer et al[15] reported that dynamic changes still occur beyond 5 years and that prevalence of GH deficiency increases. New evidence from prospective studies will contribute to obtain more precise screening algorithms.

Treatment Strategies

Central Adrenal Insufficiency

Treatment of central adrenal insufficiency in TBI patients is not different from other etiologies and the relevant guidelines should be followed.[35] In urgent cases with suspected adrenal crisis, parenteral hydrocortisone (100 mg followed by 200 mg/24 h) should be started immediately.[53]

For daily replacement, hydrocortisone at a dose of 5-10 mg/m^2 is recommended.[35] The dose should be adjusted according to clinical evaluation and comorbid conditions. The total dose is divided, and the higher dose should be taken in the morning. Patients should be taught about the risk of adrenal crisis and stress dosing. They should be provided injectable glucocorticoid emergency kits and informative alert cards or other identification.[35]

Central Hypothyroidism

The use of levothyroxine is recommended for replacement therapy in central hypothyroidism.[35] The daily dose of levothyroxine approximates 1.6 μg/kg/day, and it should be adjusted aiming at the upper half of the reference range of serum-free T4 levels.[35] Clinicians should consider the age and comorbid diseases of the patient when deciding on the starting dose and adjusting during follow-up.

Central Hypogonadism

Patients should be started on gonadal hormone replacement during the chronic phase following TBI.[4] The combined estrogen and progesterone replacement should be prescribed to adult pre-menopausal female patients to restore menstrual cycles as well as to prevent bone loss and decrease cardiovascular risk.[35] It is recommended to continue replacement until the age of menopause.[35]

Testosterone replacement is recommended for male patients with central hypogonadism following TBI. Restoring normal serum testosterone levels will improve muscle mass, body composition, anemia, sexual function, sense of well-being, and quality of life.[35]

Clinicians should be aware of contraindications while prescribing gonadal hormones and also keep in mind the possibility of reversibility of pituitary–gonadal axis dysfunction in patients following TBI. The replacement therapy was withdrawn and the patient was re-evaluated during follow-up.

Growth Hormone Deficiency

Growth hormone replacement is generally suggested to be started at least 1 year following TBI.[4] The functioning of the axis is likely reversible during the first year, and also there is a lack of evidence regarding the beneficial effects of GH shortly after trauma. Levels of evidence for recommendations to start GH replacement depend on the age of the patient. In adolescents and during the transition period, GH replacement is strongly suggested due to the beneficial effects on peak bone mass, while there is a paucity of data regarding patients older than 80 years.[41] The decision for replacement in adult patients is mainly based on clinical evaluation. Patients with symptoms suggestive of GH deficiency such as impairments in body composition, memory problems, or low QoL should be offered GH replacement. A low QoL–AGHDA score is required by reimbursement policies in some countries, while in Turkey the only requirement is biochemical verification of GH deficiency.

A recent meta-analysis showed that GH replacement in GH-deficient TBI patients during the chronic phase decreased the severity of depression and improved cognitive functions (memory and processing speed) and also QoL.[54] Increase in cardiorespiratory fitness and improvement in symptoms related to fatigue and depression were reported in another study.[55] Increase in muscle mass and a decrease in fat mass are also among the expected beneficial effects of GH replacement.[41]

The dosing in adults depends on the age and gender of the patient.[41] The starting dose in patients aged 30-60 years is 0.2-0.3 mg/day and 0.1-0.2 mg/day in those older than 60 years.[41] Serum IGF-1 levels should be monitored and the dose of GH therapy titrated accordingly aiming upper half of IGF-1 reference range.[41] Dose adjustments of glucocorticoid and thyroid hormones might be needed after GH therapy.[41] Improvement in QoL may be objectively measured by the use of QoL–Adult Growth Hormone Deficiency Assessment (AGHDA) scoring system.[56] However, as it might not be translated into other languages, the follow-up is based on clinical evaluation. The replacement may be stopped if no improvements are observed following therapy of 1 year.[41] Growth hormone replacement is contraindicated in patients with active malignancy.

Interestingly, patients with various neurologic disabilities following TBI improved under GH therapy regardless of being GH deficient.[57] The authors stated that GH induced neurogenesis and neural plasticity.[57] There is a need for further studies validating beneficial effects and analyzing safety before clinical use.

Diabetes Insipidus

The mainstay of treatment of central DI is the replacement of water deficit and appropriate dosing of desmopressin. Oral and nasal

formulations can be started in outpatient settings and parenteral forms can be used for internalized patients.[50] The dose requirements depend on the remaining endogenous hormone reserve.[50] The daily dose of oral tablets might range widely from 100 µg/day to 600 µg/day. Nasal forms have a more rapid onset of action compared to oral forms. Hyponatremia can ensue with desmopressin therapy and excessive water intake. In order to prevent hyponatremia, withholding desmopressin dose until increase in diuresis or omitting therapy 1 day weakly on a regular basis is recommended.[50]

Future Perspectives

There is a need for precise markers predicting the risk of pituitary dysfunction after TBI. Previous studies reported an association between serum and cerebrospinal fluid levels of markers such as glial fibrillary acidic protein, neurofilaments, and total tau protein.[58] These markers might also be useful for the prediction of pituitary dysfunction following TBI. Prospective studies are needed to test this assumption. There has been only one study analyzing the association between microRNAs and pituitary dysfunction following TBI.[26] The results of this preliminary study imply that novel markers could be derived from microRNAs.

In recent years, studies reported highly interesting data regarding the associations between TBIs and microbiota–gut–brain axis. Traumatic brain injury may cause dysbiosis of the gut microbiome which is further associated with the development of neurodegenerative diseases.[59] Moreover, impairment of the GH/IGF-1 axis following TBI was also reported to cause gut dysbiosis.[60] There seems to exist a bidirectional and dynamic relationship between the GH axis and gut microbiome, and that microbiome contributes to neurocognitive improvements during GH replacement in patients with GH deficiency following TBI.[60] Further research on this interesting area will provide more data regarding pathogenesis and clinical implications.

Some recent studies reported the successful use of machine learning systems in predicting the outcome, discharge rates, and mortality following TBI.[61,62] Clinical characteristics, the severity of TBI, as well as various radiologic features have been tested as predictors in studies using artificial intelligence algorithms.[63] A recent study by Ko et al[64] reported an association between microRNAs packed in brain-derived extracellular vesicles and the state of TBI implementing machine learning. However, much more remains to be done before implementing this novel technology in everyday clinical practice regarding TBI. On the other hand, there have been no studies investigating the use of machine learning systems in terms of predicting pituitary dysfunction following TBI. Artificial intelligence algorithms might play an important role in the precise selection of patients to be screened for pituitary dysfunction after TBI.

Conclusion

The diagnosis of pituitary dysfunction following TBI might be challenging. Despite a rapidly growing literature on the issue, there are still gaps in guidance and inconsistencies between recommendations due to a lack of strong predictive markers. Until more precise risk factors and new screening algorithms emerge, clinicians should follow current recommendations regarding routine screening of pituitary dysfunction following TBI. Timely diagnosis of pituitary dysfunction is of utmost importance as it may be not only life-saving but also life-changing through significant impact on QoL.

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