

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
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DISEASE STATE CLINICAL REVIEW:
A NEUROENDOCRINE APPROACH TO
PATIENTS WITH TRAUMATIC BRAIN INJURY

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ABSTRACT

Objective: Traumatic brain injury (TBI) is now recognized as a major public health concern in the United States and is associated with substantial morbidity and mortality in both children and adults. Several lines of evidence indicate that TBI-induced hypopituitarism is not infrequent in TBI survivors and may contribute to the burden of illness in this population. The goal of this article is to review the published data and propose an approach for the neuroendocrine evaluation and management of these patients.

Methods: To identify pertinent articles, electronic literature searches were conducted using the following keywords: “traumatic brain injury,” “pituitary,” “hypopituitarism,” “growth hormone deficiency,” “hypogonadism,” “hypoadrenalism,” and “hypothyroidism.” Relevant articles were identified and considered for inclusion in the present article.

Results: TBI-induced hypopituitarism appears to be more common in patients with severe TBI. However, patients with mild TBI or those with repeated, sports-, or blast-related TBI are also at risk for hypopituitarism. Deficiencies of growth hormone and gonadotropins appear to be most common and have been associated with increased morbidity in this population. A systematic approach is advised in order to establish the presence of pituitary hormone deficiencies and implement appropriate replacement therapies.

Conclusion: The presence of traumatic hypopituitarism should be considered during the acute phase as well as during the rehabilitation phase of patients with TBI. All patients with moderate to severe TBI require evaluation of pituitary function. In addition, symptomatic patients with mild TBI and impaired quality of life are at risk for hypopituitarism and should be offered neuroendocrine testing. (*Endocr Pract.* 2015;21:823-831)

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This review article is a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with, and not a replacement for, their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

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Abbreviations:

CBG = corticosteroid-binding globulin; DI = diabetes insipidus; GH = growth hormone; IGF-1 = insulin-like growth factor 1; SIADH = syndrome of inappropriate antidiuretic hormone; T₄ = thyroxine; TBI = traumatic brain injury; TSH = thyroid-stimulating hormone

INTRODUCTION

Traumatic brain injury (TBI) is a major public health concern in the United States and other Western countries and accounts for substantial morbidity and mortality in both children and adults (1). There is evidence to suggest that

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TBI-induced hypopituitarism is common and is associated with substantial morbidity, increased mortality, as well as long-term disability in this population (2).

The present article aims to review data on the epidemiology of traumatic hypopituitarism, the underlying pathophysiology and pertinent pathologic findings, as well as discuss the clinical presentation, diagnosis, and neuroendocrine management of adult patients with TBI. Areas of uncertainty will be highlighted, including the pathogenesis and natural history of TBI-induced hypopituitarism, limitations of endocrine testing, as well as risks and benefits of replacement therapies with regards to rehabilitation outcomes.

METHODS

To identify pertinent articles, electronic literature searches were conducted using the following keywords: “traumatic brain injury,” “pituitary,” “hypopituitarism,” “growth hormone deficiency,” “hypogonadism,” “hypoadrenalism,” and “hypothyroidism.” Articles were included in the reference list based on recommendations by committee members. Citations were not graded for quality. Only articles in English were included in the reference list. The present article represents a nonsystematic review article and reflects the informed opinions of the Neuroendocrine and Pituitary Scientific Committee members.

DISCUSSION

Epidemiology

It has been estimated that approximately 1.7 million people with TBI are evaluated in United States hospitals annually, and approximately 52,000 patients die each year as a result of TBI (1). The estimated burden of long-term disability related to TBI is even greater, affecting approximately 5.3 million individuals in the United States (1). Furthermore, it is likely that TBI is underreported, particularly among patients with mild TBI or those with sports-related injuries, many of whom may suffer repeated head trauma (3). In the acute phase, access to health care may be limited in war zones, which may further contribute to underreporting of TBI in these settings.

TBI is recognized as a common cause of death and disability in adults, children, and young adults, with consequences ranging from physical disabilities to long-term cognitive, behavioral, psychological, and social defects (4). Motor vehicle accidents, including pedestrian-car and bicycle-car encounters, falls, child abuse, violence, and sports injuries are the commonly implicated causes of TBI-associated pituitary dysfunction (1). In the military, blast injuries have been recently recognized as a cause of TBI-induced hypopituitarism (5-7). Groups at high risk for TBI include males, young adults 15 to 24 years of age, children less than 5 years of age, and elderly persons over 75 years of age (8).

Estimates of the prevalence of hypopituitarism in patients with TBI vary widely between studies, ranging between 15 and 68% of patients (2,9). These wide variations likely reflect the presence of considerable heterogeneity between study populations, types and severity of injury, timing of the assessment, diagnostic criteria, and the confounding effects of intercurrent illness, medications, and nutrition status. In a systematic review of 14 studies reporting data on 1,014 patients, the prevalence of hypopituitarism was 35.3, 10.9, and 16.8% in patients with severe, moderate, and mild TBI, respectively (2). Among 809 patients who were tested at least 5 months after their sentinel injury, growth hormone (GH) deficiency and gonadotropin (follicle-stimulating hormone/luteinizing hormone) deficiency were most prevalent, each affecting 12% of patients (2). Adrenocorticotropic hormone (ACTH) deficiency was reported in 8% and thyroid-stimulating hormone (TSH) deficiency was present in 4% of patients. Multiple pituitary hormone deficiencies were present in 8% of patients. Of note, some recovery of pituitary function occurred, but new pituitary hormone deficiencies also developed during follow-up in some patients. Among 240 patients studied prospectively, there were 50 new hormone deficiencies and 113 recoveries of an endocrine axis by 12 months after TBI (2). There are limited data regarding the natural history of hypopituitarism several years after TBI (10).

In a more recently published systematic review of 66 studies (5,386 adult patients), the prevalence of persistent anterior pituitary hormone deficiencies was approximately 30% (11). Hypopituitarism was associated with higher mortality in the intensive care unit (ICU) in this analysis. Older patients and those who have suffered skull-base fractures or more severe TBI appear to be at higher risk of hypopituitarism (11).

In children, a recent prospective study evaluated pituitary function after TBI and found that the prevalence of neuroendocrine dysfunction was 15% at 1 month, 75% at 6 months, and 29% at 12 months. At 1 year after TBI, 14% had precocious puberty, 9% had hypothyroidism, and 5% had GH deficiency (12). A study of 23 patients in the transition period (ages 16 to 25 years) found that hypopituitarism was present in 34.6% at 3 months after TBI, and at 12 months, hypopituitarism was present in 30.3% (13). On the other hand, the prevalence of hypopituitarism was only 8% in a study of 87 children and adolescents who were evaluated at 12 months after severe TBI (14), whereas in another study of 198 children with remote history of TBI in early childhood, low peak stimulated GH and cortisol levels were found in only 8% of the subjects (15).

Pathophysiology and Pathology

The pathophysiology of hypopituitarism in patients with TBI remains incompletely understood and is likely multifactorial (16,17). Pathologic data include the presence of necrosis, fibrosis, infarction, and hemorrhage in the

pituitary gland of patients dying from nonpenetrating head injuries (17,18). Several potential mechanisms have been proposed to explain the development of hypopituitarism in patients with TBI, including direct injury to the hypothalamo-hypophyseal unit and/or its blood supply, compression of the pituitary as a result of edema, hemorrhage or elevated intracranial pressure, and trauma-related anemia, hypotensive and/or hypoxic insults (17). The hypophyseal portal vessels passing through the diaphragma sella to supply the anterior pituitary are particularly susceptible to mechanical injury and compression, including those from direct shearing forces, local parasellar brain swelling and brain hemorrhage, raised intracranial pressure, and vasospasm.

Genetic factors, including the presence of certain apolipoprotein E haplotypes, some of which have also been associated with increased risk of Alzheimer's disease, might also influence the risk of developing traumatic hypopituitarism (19). This observation is preliminary and requires confirmation in additional studies. The presence of antipituitary and antihypothalamic antibodies has been reported in patients with TBI in a preliminary study (20). However, their potential pathogenic role remains obscure and requires further study. Smaller hippocampal volumes have been reported in football players with a history of mild TBI, a finding that could be potentially associated with abnormalities in attention, memory, and dysregulation of the pituitary adrenal axis (21). It is clear that additional research is needed in order to fully elucidate the underlying mechanisms of hypopituitarism in patients with TBI.

Clinical Presentation and Diagnosis

All patients with moderate to severe TBI should be evaluated for hypopituitarism during the acute and chronic course of their recovery (22). In general, the major focus during the first 2 weeks postinjury should be on the adrenal axis and posterior pituitary function. In the subsequent months after injury, the entire anterior and posterior pituitary hormonal axes should be assessed. In addition, symptomatic patients with mild TBI (including those with repetitive mild TBI) and impaired quality of life are also at risk for hypopituitarism and should be offered neuroendocrine testing (Table 1) (3). The severity of TBI can be categorized using the classification proposed by the U.S. Department of Defense (Table 2) (23).

Acute Hypopituitarism

Central hypoadrenalism and diabetes insipidus (DI) may manifest in the acute phase after TBI, particularly in moderate and severe TBI, and should be considered early in the neuroendocrine evaluation of these patients (22,24). Up to 50% of hospitalized moderate or severe TBI patients may develop central hypoadrenalism, which can be associated with severe anemia, hypotension or hypoxia, as well as hyponatremia (24,25). Low serum cortisol levels have been associated with increased mortality in patients with moder-

ate to severe TBI (26). In contrast to Addison's disease, skin hyperpigmentation and hyperkalemia are notably absent in patients with TBI-induced hypopituitarism, who lack both ACTH and cortisol but have sufficient aldosterone secretion.

Morning serum cortisol levels ≥ 18 $\mu\text{g/dL}$ generally assure sufficient function of the hypothalamic-pituitary-adrenal axis (25,27). Of note, lower cut points have been proposed in some studies (25,28). Caution is advised in interpreting serum cortisol levels, as they can be influenced by abnormalities in corticosteroid-binding globulin (CBG) levels. Examples include high serum CBG levels in women taking oral estrogen (or during pregnancy) and low CBG levels in patients with acute illness and malnutrition. In the acute ICU-phase of injury, cortisol levels can also be significantly suppressed by commonly used medications, including etomidate and metabolic suppressive agents such as pentobarbital and propofol (24).

Morning serum cortisol levels ≤ 3 $\mu\text{g/dL}$ are diagnostic of adrenal insufficiency. Patients with intermediate morning cortisol levels (3.1 to 17.9 $\mu\text{g/dL}$) may also have hypoadrenalism and should be considered as candidates for glucocorticoid replacement in the presence of suggestive clinical findings. These patients require dynamic testing to fully evaluate their hypothalamic-pituitary-adrenal function in the chronic phase after TBI. It has also been proposed that all hospitalized patients with moderate to severe TBI and morning serum cortisol < 10 $\mu\text{g/dL}$ be administered glucocorticoid replacement in the acute phase after TBI (22,26).

Posterior Pituitary Function Testing: Central DI should be suspected in the presence of polyuria (urine output > 200 mL/hour for at least 2 hours or 40 mL/kg/24 hours (> 3 L/24 hours in patients of average weight) and/or hypernatremia (29,30). These patients are at risk for dehydration if their sensorium is clouded, they lack access to water, or suffer from hypodipsia or adipsia. The presence of DI has been associated with increased mortality in patients with moderate to severe TBI (26).

Among patients with hypernatremia who have not received diuretics or mannitol, the presence of inappropriately dilute urine (< 700 mOsm/kg) is consistent with the diagnosis of DI. The water deprivation test can help establish the diagnosis of central DI and differentiate this condition from nephrogenic DI or primary polydipsia (29). Safety considerations suggest that this test only be performed in stable patients in a monitored setting. Measuring plasma arginine vasopressin may potentially be of diagnostic value during the water deprivation test, but this assay is often fraught with technical difficulties in usual clinical settings and its use cannot be recommended. Measuring serum copeptin, the C-terminal portion of the vasopressin precursor that is secreted in equimolar ratio to vasopressin, appears to be helpful in the differential diagnosis of hypernatremic disorders (31,32). This assay is currently available in some European countries but not in the United States. Pituitary imaging (magnetic resonance imaging [MRI]) generally

Table 1
Diagnostic Criteria for Hypopituitarism in Adults

Pituitary function	Test	Interpretation
Pituitary adrenal axis	Morning serum cortisol	Morning serum cortisol ≤ 3 $\mu\text{g/dL}$ is diagnostic of hypoadrenalism; serum cortisol ≥ 18 $\mu\text{g/dL}$ assures sufficient function; intermediate levels require further evaluation
	Cosyntropin stimulation test ^a	Peak serum cortisol < 18 $\mu\text{g/dL}$ is diagnostic of hypoadrenalism
	Insulin tolerance test	Peak serum cortisol < 18 $\mu\text{g/dL}$ is diagnostic of hypoadrenalism
	ACTH	Low or inappropriately normal levels in patients with central hypoadrenalism
Pituitary thyroid axis	Free T ₄	Low in patients with hypothyroidism
	TSH	Low or inappropriately normal levels in patients with central hypothyroidism
Pituitary gonadal axis	Total testosterone and SHBG (or free testosterone) in men; estradiol in women	Low sex steroid levels in patients with hypogonadism (obtaining a menstrual history is essential in women)
	FSH, LH	Low or inappropriately normal levels in patients with central hypogonadism
GH	IGF-1	Low age- and gender-adjusted levels in patients with history of pituitary insult and ≥ 3 additional pituitary deficiencies are diagnostic of GH deficiency
	Insulin tolerance test or glucagon stimulation test	Peak GH < 3 ng/mL is diagnostic of GH deficiency ^b
	GHRH-arginine stimulation test	Peak GH < 11.5 ng/mL is diagnostic of GH deficiency in patients with BMI < 25 kg/m ² Peak GH < 8 ng/mL is diagnostic of GH deficiency in patients with BMI 25-30 kg/m ² Peak GH < 4.2 ng/mL is diagnostic of GH deficiency in patients with BMI > 30 kg/m ²
Posterior pituitary function	Serum sodium and urine osmolality	Hypernatremia and urine osmolality < 700 mOsm/kg are consistent with DI in polyuric patients
	Water deprivation test	Hypernatremia and peak urine osmolality < 700 mOsm/kg are consistent with DI in polyuric patients; response to desmopressin administration helps differentiate between central and nephrogenic DI

Abbreviations: ACTH = adrenocorticotropic hormone; BMI = body mass index; DI = diabetes insipidus; FSH = follicle-stimulating hormone; GH = growth hormone; GHRH = growth hormone–releasing hormone; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; TSH = thyroid-stimulating hormone; T₄ = thyroxine.

^aThis test may not be reliable for several weeks after traumatic brain injury and is not recommended in the acute phase.

^bLower cut points for the glucagon stimulation test have recently been proposed in obese or overweight adults (56).

Variable	Mild	Moderate	Severe
Glasgow coma scale	13-15	9-12	3-8
Alteration of consciousness	≤24 h	>24 h	>24 h
Loss of consciousness	0-30 min	>30 min but <24 h	≥24 h
Posttraumatic amnesia	≤24 h	>24 h but <7 days	≥7 days

reveals an absence of the “posterior bright spot” in unenhanced T1-weighted sequences in patients with central DI and may also show stalk disruption. Pituitary imaging additionally serves to exclude a nonadenomatous (or rarely, adenomatous) sellar mass as the cause of DI.

Hyponatremia is common in patients with TBI and is most frequently caused by the syndrome of inappropriate antidiuretic hormone (SIADH) secretion (30,33). However, caution is advised in order to exclude other possible causes, including adrenal insufficiency, hypothyroidism, hypovolemia, volume overload states, and medication side effects as contributing factors before attributing hyponatremia to SIADH.

Chronic Hypopituitarism **(3 months or later after TBI) (2)**

The symptoms and signs of hypopituitarism are not unique to pituitary dysfunction caused by TBI. Patients with central hypoadrenalism may also present more indolently with fatigue, weight loss, anorexia, dizziness, and joint aches several weeks or months after TBI. Although dynamic testing of pituitary adrenal function is not recommended during the acute phase after TBI, it can be helpful in establishing the diagnosis of central hypoadrenalism in stable patients several weeks after injury (22). The cosyntropin stimulation test directly assesses adrenocortical responsiveness, and a blunted response suggests the development of adrenocortical atrophy (occurring as a result of corticotropin deficiency) (25). As a corollary, it may take 6 to 8 weeks after TBI for patients with central hypoadrenalism to show an abnormally low cortisol response on this test. Other dynamic tests of pituitary adrenal function, including the insulin tolerance test or the metyrapone test, can be helpful in assessing adrenal reserve in the chronic phase but may not be practical or safe in acutely ill patients. In addition, the insulin tolerance test is contraindicated in patients with seizures, cardiovascular disease, or advanced age.

Patients with central hypothyroidism are unlikely to present during the acute phase after TBI (owing to the long half-life of thyroxine) (22,25). These patients may present with typical hypothyroid symptoms, including fatigue,

weight gain, constipation, irregular menses, cold intolerance, neurocognitive dysfunction, depression, and hyponatremia, but notably lack a goiter (in contrast to patients with Hashimoto’s disease).

Laboratory testing in patients with central hypothyroidism demonstrates low serum free thyroxine (T_4) levels with either low or inappropriately normal serum TSH levels (25). Of note, triiodothyronine (T_3) levels are generally maintained in the normal range in patients with hypothyroidism. Acutely ill hospitalized patients often show abnormalities in thyroid function tests (“euthyroid sick syndrome”), which can be difficult to distinguish from true central hypothyroidism. In patients with euthyroid sick syndrome, T_3 levels are usually low, but T_4 levels may also decline in the presence of critical illness (34). To avoid diagnostic confusion, evaluation of hypothalamic-pituitary-thyroid function may generally be deferred for several (≥ 4 to 6) weeks after TBI in the absence of known or suspected pre-existing hypothyroidism.

The evaluation of the pituitary gonadal axis is appropriate only in stable outpatients during the rehabilitation phase after TBI, as acute illness or injury will generally result in suppression of gonadal function (22,25,35). Patients may present with sexual dysfunction, amenorrhea (women), and (occasionally) hot flashes. Loss of secondary hair and bone mass may result. Of note, hypogonadal patients with a history of moderate to severe TBI appear to be less likely to gain functional independence during rehabilitation (36).

To examine the possibility of central hypogonadism in men, morning serum testosterone levels should be measured (25,37). Abnormal results should be confirmed by repeat testing. In premenopausal women, the evaluation includes assessment of menstrual history for evaluation of hypogonadism. In patients of both genders with symptoms of hypogonadism and low serum sex steroid levels, the presence of low or inappropriately normal serum gonadotropins helps to establish the diagnosis of central hypogonadism. Evaluation of the pituitary gonadal axis can be confounded by the suppressive effects of several medications, including opioids and glucocorticoids in pharmacologic doses. Hyperprolactinemia may also occur (in 11.8% of patients

with TBI in one study) (38) as a consequence of hypothalamic dysfunction, stalk interruption, and/or medication side effects and can be a contributing factor to the development of hypogonadism.

Assessment of GH secretion should also be deferred for several months after TBI and should be conducted in patients whose other pituitary deficiencies have been replaced (25,39). Adult patients with GH deficiency may report poor stamina and exercise capacity, impaired quality of life, central adiposity and may develop dyslipidemia, insulin resistance, and low bone mass (40). Patients with TBI and GH deficiency may also report decreased memory and attention (40). Decreased linear growth is likely to occur in GH-deficient children or adolescents (41).

Randomly measured serum GH levels are of no diagnostic value in the assessment of GH secretion, as healthy adults often have undetectable random GH levels during the daytime (39). Serum insulin-like growth factor 1 (IGF-1) levels lack sensitivity in the diagnosis of GH deficiency in adults (39). On the other hand, low serum IGF-1 levels can also be present in patients taking oral estrogen and those with liver disease or poorly controlled diabetes mellitus. However, patients with a known pituitary insult, low serum IGF-1 levels, and multiple (≥ 3) additional pituitary hormone deficiencies are very likely to be GH deficient (39).

In all other cases, a GH stimulation test is required in order to make the diagnosis of GH deficiency (39,42). Agents used to stimulate GH secretion include insulin, glucagon, growth hormone–releasing hormone (GHRH) plus arginine, arginine alone, or ghrelin mimetics (43,44). In the U.S., GHRH is currently not commercially available, and ghrelin mimetics have not been Food and Drug Administration–approved for testing. In addition, insulin tolerance testing is contraindicated in some patients (as already noted) and requires close physician monitoring to assure patient safety. With the limitations of the insulin tolerance test, the glucagon stimulation test has therefore now emerged as the preferred alternative test used to diagnose GH deficiency in adults because of its availability, safety, lack of influence by gender and hypothalamic cause of GH deficiency, and relatively few contraindications (39). In contrast, the glucagon stimulation test lacks specificity in the diagnosis of central hypoadrenalism in adults, as the cortisol response to glucagon administration is often low in patients without adrenal dysfunction (45).

Patients with evidence of hypopituitarism should undergo pituitary imaging (MRI) to exclude the presence of a sellar mass (25,39). Periodic reassessment of pituitary function is advised in patients with history of TBI in order to detect possible recovery of pituitary hormone deficiencies or the development of additional pituitary hormone deficits. Adult patients seen in the acute phase after TBI may be re-evaluated at 2 to 6 months and 12 months (7,46,47). Recommendations regarding long-term retesting of pituitary

function (>12 months after TBI) cannot be made in the absence of sufficient data.

In children, neuroendocrine dysfunction is common after TBI, can evolve after injury, and can be persistent. Thus, every child with a moderate or severe head injury should undergo routine neuroendocrine surveillance until at least 1 year after injury, even if there are no abnormal findings at 6 months. Most, but not all, endocrine abnormalities resolve by 1 year after TBI. New endocrinopathies may be identified at 6 to 12 months after injury in children and are mostly transient and isolated. Therefore, we recommend ongoing neuroendocrine surveillance at both 6 and 12 months after TBI to document resolution of temporary abnormalities and to ensure early intervention for persistent or late-occurring endocrinopathies in both children and adults.

Management

Prompt institution of glucocorticoid replacement is critical in patients with known or suspected central hypoadrenalism (22,26). Acutely ill patients with suspected hypoadrenalism should receive glucocorticoids in stress doses (i.e., hydrocortisone 100 mg intravenously every 6 to 8 hours) without awaiting biochemical confirmation of the diagnosis. Stable patients with central hypoadrenalism can be treated with hydrocortisone (15 to 25 mg/daily in divided doses) or prednisone (2.5 to 5.0 mg daily), titrated based on clinical criteria. These patients do not need mineralocorticoid replacement, as aldosterone secretion is preserved.

Patients with central DI can be treated with desmopressin. In hospitalized patients, desmopressin should be administered on demand (1 to 2 μ g subcutaneously or intravenously every 8 to 12 hours as needed), as central DI is often transient (22). Careful monitoring of fluid balance and serum sodium is required in order to avoid hyponatremia. Stable outpatients can be treated with oral or nasal desmopressin (10 to 20 μ g nasally or 100 to 400 μ g orally administered every 8 to 24 hours), titrated to maintain comfortable sleep and permit daytime activities without polyuria or excessive thirst, while maintaining eunatremia. Allowing the medication effect to wear off between doses can be helpful in order to avoid hyponatremia. Drinking to thirst only is advised in the majority of patients with central DI who have intact thirst. In contrast, patients with adipsia or hypodipsia require careful monitoring of fluid balance and sodium levels and generally need to drink fluids on schedule in order to avoid abnormalities of salt and water homeostasis.

Patients with central hypothyroidism can be treated with levothyroxine replacement at a mean full replacement dose of approximately 1.6 μ g/kg/day (25). A lower starting dose is appropriate in older patients and those with cardiovascular disease or mild hypothyroidism. To avoid precipitating adrenal crisis, levothyroxine replacement should commence only after adrenal function has been assured to be intact or replaced with glucocorticoids. Serum free T_4 levels (not

TSH) should be monitored at 6 weeks after starting levothyroxine replacement with a goal of maintaining them in the middle of the normal range (25).

Patients with central hypogonadism who are not pursuing fertility can receive sex steroid replacement, if not contraindicated (25). It is not known whether testosterone replacement may help improve the functional independence of patients with TBI in rehabilitation. In men, testosterone replacement can be administered as transdermal gels, patches, buccal or subcutaneous pellets, or intramuscular injections (37). As the cardiovascular safety of testosterone replacement in older men, particularly those with cardiovascular disease, has been called into question in recent observational studies, caution is advised before considering testosterone replacement in these groups until more definitive data from clinical trials become available (48,49). Women of premenopausal age who have central hypogonadism can receive estrogen and progestin replacement (if they have an intact uterus) or estrogen replacement only (after hysterectomy), if not contraindicated, based on careful gynecologic evaluation and follow-up.

If not contraindicated, GH replacement may be implemented in GH-deficient patients after other pituitary hormone deficiencies have been addressed (25,39,41). Preliminary studies suggest a possible benefit of GH replacement on cognition and quality of life in patients with TBI (50-54). However, additional studies are needed to establish any potential benefits of GH replacement on neurocognitive function in this population. In addition, GH replacement may improve body composition (increasing muscle and bone mass and decreasing visceral adiposity), cardiovascular risk factors (including serum lipids and C-reactive protein), and exercise capacity (39). Lower starting doses are advisable in older patients, who are more prone to develop side effects (such as arthralgias, edema, or carpal tunnel syndrome). Monitoring also includes serum IGF-1 levels, which are helpful in order to titrate GH doses (targeting IGF-1 levels between 0 to +1 standard deviation score) (39). Hyperglycemia may occur, particularly in obese patients, as a result of the direct effects of GH on glucose homeostasis. Thus, glycemic monitoring is advisable in patients receiving GH replacement. In addition, GH replacement may unmask latent hypoadrenalism, increase requirements for levothyroxine replacement, or decrease requirements for desmopressin, mandating careful monitoring and possible adjustments in these replacement therapies (25,39).

CONCLUSION

Over the past several years, a substantial body of evidence has suggested that TBI-induced hypopituitarism is not uncommon and is associated with increased morbidity and mortality in this population. While patients with moderate and severe TBI appear to be at higher risk, patients with mild or repetitive TBI may also develop pituitary hormone

deficiencies (2,55). A thorough, systematic evaluation of pituitary function is advisable in patients with moderate to severe TBI as well as symptomatic patients with mild TBI and impaired quality of life, aiming at detecting and replacing pituitary hormone deficiencies in the hopes of improving patient outcomes. Acutely, during the hospitalization phase of injury, the focus should be on monitoring for adrenal insufficiency, DI, and SIADH. In the chronic phase, the entire anterior and posterior pituitary function should be examined, including assessments for GH-deficiency and hypogonadism, which appear to be most common, as well as assessments of adrenal and thyroid function.

Further research is needed to characterize the natural history of TBI-induced hypopituitarism, identify pertinent risk factors, elucidate the underlying pathophysiology, and establish the risks and benefits of replacement therapies in this patient population with regards to rehabilitation outcomes and quality of life.

DISCLOSURE

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