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Neuroendocrine Disruptions Following Head Injury

Tamara L. Wexler[1,2]

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Abstract

Purpose of Review This article reviews hypopituitarism after TBI, the importance of pituitary hormones, and related controversies, concluding with a suggested patient approach.

Recent Findings While earlier studies focused on increased pituitary deficiencies after moderate-severe TBI, recent studies have focused on deficiencies after mild TBI. There has been increasing focus on the role of growth hormone after injury; growth hormone is the most frequent reported deficiency at 1 year post-TBI, and an area with unresolved questions. While more research is needed to quantify the risk of deficiencies in special populations, and establish the natural history, increasing data indicate an increase in hypopituitarism after other acquired brain injuries; the potential role of pituitary hormone deficiencies after stroke and after COVID-19 infection is an area of active inquiry.

Summary Given the negative health effects of untreated hypopituitarism and the opportunity to intervene via hormone replacement, it is important to recognize the role of pituitary hormone deficiencies after TBI.

Keywords Hypopituitarism · Pituitary deficiencies · Neuroendocrine · Growth hormone · TBI · COVID-19

Introduction

While increasing attention is being paid to the long-term health effects that may occur after head injuries, the role that neuroendocrine dysfunction may play in patients' health after traumatic brain injury (TBI) remains underappreciated. Even mild TBI confers an increased risk for chronic anterior pituitary hormone deficiencies, which may appear at a delay. Awareness of the potential contribution of pituitary deficiencies to lingering symptoms following TBI is crucial: undiagnosed and untreated deficiencies confer increased morbidity and mortality, which can be reversed by appropriate hormone replacement.

This article will review existing evidence for the increase in neuroendocrine deficiencies seen after TBI, the role of pituitary hormones and symptoms of pituitary hormone deficiencies, and current issues in this field, and will close with a suggested practical approach to patients. Because long-term neuroendocrine effects following TBI consist primarily of deficiencies in anterior pituitary hormones that arise more than three months following the injury, we focus on this "chronic" period after briefly addressing clinically relevant (and typically transient) neuroendocrine deficiencies in the acute post-TBI period. The anterior pituitary regulates the cortisol, thyroid hormone, sex hormone, and growth hormone axes.

Pituitary Deficiencies After TBI: What We Know

Acute Neuroendocrine Dysfunction After TBI

In the acute period after TBI, it is important to consider adrenal insufficiency due to alterations in the adrenocorticotropic hormone (ACTH)-cortisol axis, but there is no clear role for evaluating the other anterior pituitary axes (thyroid, sex hormone, and growth hormone) as changes are thought to serve a compensatory purpose and may be temporary[1, 2]. A wide range of reported rates for the prevalence of adrenal insufficiency in the acute period—9.8–78% [1,

✉ Tamara L. Wexler
tamara.wexler@nyulangone.org

[1] Department of Rehabilitation Medicine, NYU Grossman School of Medicine, 240 E 38th St 15th Floor, New York, NY 10016, USA

[2] Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

3–5]—reflects different cortisol thresholds used to define adrenal insufficiency (AI), as well as the diagnostic test employed and time since injury: rates are higher in studies measuring cortisol levels more proximal to injury and using higher thresholds for AI. Interestingly, cortisol levels deemed consistent with acute AI did not lead to cortisol replacement in many studies which treated only a subset of patients. This may reflect uncertainty in diagnosis, as provocative testing (such as the cosyntropin stimulation test, the gold standard in the chronic period) is not reliable in the first 6 weeks after an injury, and practices vary as to what baseline morning cortisol value should prompt consideration for treatment, with heavy reliance on clinical symptoms [3, 4, 6–8]. The majority of subjects with low cortisol levels recovered during the study periods of monitoring, underscoring the importance of repeating an evaluation at > 3 months [3, 4]. Notably, acute AI after TBI does not correlate with chronic AI in adults [3, 4, 9, 10] or children [11].

Posterior pituitary hormones may also be affected in the acute period, most often transiently. Clinically apparent posterior pituitary dysfunction primarily occurs as a deficiency or excess in vasopressin (also known as antidiuretic hormone or ADH), i.e., diabetes insipidus (DI) or the syndrome of inappropriate antidiuretic hormone (SIADH); monitoring of sodium levels and urine output is indicated. Central DI, or arginine vasopressin deficiency (AVP-D), has been described in 14–26% of patients in the acute period after TBI [12–14]. Interestingly, a number of studies have reported that central DI/AVP-D is associated with mortality [3, 9, 12, 13]. This association may be related to increased intracranial pressure, for which central DI/AVP-D may be a marker. SIADH has been reported in recent decades to appear in 2.5–14% of post-TBI patients in the acute period [1, 13, 14], including immediately following transient DI. Clinically, SIADH appears as euvolemic hyponatremia with serum hypoosmolality and urine hyperosmolarity, in the absence of any other known cause. Hyponatremia may also occur soon after TBI for other reasons, including adrenal insufficiency and dehydration, and it is important to rule out other causes as contributing factors. The "triphasic response," in which transient DI is followed by transient SIADH with some patients then progressing to persistent central DI, has been occasionally described after TBI [15, 16].

Chronic Neuroendocrine Deficiencies After TBI

Long-term neuroendocrine effects following TBI consist primarily of deficiencies in anterior pituitary hormones that arise in the "chronic" period, more than 3 months after injury. The remainder of this review thus focuses on deficiencies in the hormones produced or regulated by the anterior pituitary, including cortisol, thyroid hormone, sex hormones, and growth hormone, more than 3 months following TBI.

Epidemiology

Pituitary deficiencies are seen at a high rate in patients who have sustained TBI, with reports of chronic pituitary dysfunction in 15–60% of adults after TBI [1–5] and up to 42% of children and adolescents [6–9]. This broad range of reported incidence reflects variability in study design, including differences not only in cohort characteristics but also in diagnostic methods and thresholds, despite global consensus as to what constitutes hormone deficiencies. Taking into account guideline-based definitions, the incidence of reported anterior pituitary hormone deficiencies approximates 25–30% by 1 year after TBI. This stands in sharp contrast to the < 0.05% prevalence found in the one study of pituitary deficiencies in a healthy adult population [10].

Time Course

While deficiencies are often termed "chronic" after 3 months, they do not always persist [17]. Deficiencies, even those diagnosed in the chronic post-TBI period, may improve over time [11, 18–21].

Notably, pituitary deficiencies may also develop at a delay, appearing months to years later. A study of Taiwan health insurance records found that rates of deficiencies increased nationally over the first 5 years after TBI [22]. Compelling smaller studies have compared hormone results in patients at 3 months versus 12 months after injury. In 70 adults evaluated for anterior pituitary deficiencies both 3 and 12 months after TBI, 8% of subjects had more deficiencies at 12 months than at 3 months [23•]. Similarly, post-TBI studies of 78 adults [21] and 89 adults [24] after TBI found new deficits at 12 months compared to earlier timepoints. More recently, a study of 58 children and adolescents assessed at 3, 6, and 12 months after TBI found new hormonal deficiencies in 5 subjects at 12 months that were not present at 3 and 6 months [19].

Any pituitary hormone evaluation should be viewed as reflecting the time at which it was conducted, with consideration for repeat evaluations, particularly if symptoms change or evolve. It is important to re-evaluate any neuroendocrine dysfunction identified before 3 months, since acute dysfunction is most often transient.

Predictive Characteristics: Who Should be Screened?

Given the number of individuals impacted by traumatic brain injury, including repetitive sports injuries and mild concussions, there is a high level of interest in identifying any predictive characteristics that would allow better

identification of individuals who should be screened for pituitary deficiencies. Severity of injury, type of injury, imaging findings, and biomarkers such as antibodies against the pituitary or hypothalamus have all been investigated.

Severity of Injury is Not a Good Predictor of Endocrine Dysfunction

Earlier guidelines focused on patients after moderate or severe TBI, recommending screening only in individuals with more severe injuries or those who required hospitalization overnight [25]. It is now clear that pituitary deficiencies are seen after mild TBI [17, 26•], with indications that even repetitive sports injury may place individuals at increased risk [27]. While some studies have found a correlation between initial Glasgow Coma Scale score and the rate of subsequent hormone deficiencies in adults [28], others (including a later study by the same group) [29] have found no such association [21, 23•, 29]. In children, TBI severity has not shown any correlation with hormone deficiency rates [30–32].

Type of Injury: Pituitary Dysfunction Can Develop After Different Causes of Injury

The risk of pituitary deficiencies appears to be elevated independent of the cause of TBI. While there are fewer studies specific to the pituitary effects of TBI sustained during sports or military service, existing studies report a similar increase in hormone dysfunction.

Increased findings of pituitary deficiencies have been described following sports-related concussion, with rates ranging from 15–46% based on study design [33]. Growth hormone deficiency (GHD) is the most frequent hormonal finding [33]. One important study of retired National Football League players (30–65 years old), with poor quality of life (per the mental component score of the 36-Item Short-Form Survey) and self-reported football-related concussions without prior known pituitary issues, diagnosed GHD in a high percentage of subjects: 41.2% (28 of 68) using the standard diagnostic cutoff (peak GH < 3.0 ng/mL) and 19.1% (13 of 68) using reduced thresholds based on BMI (peak GH < 3 if BMI < 25 kg/m2; < 0.9 if BMI 25–30 kg/m2; < 0.5 if BMI > 30 kg/m2) [34•]. The study did not offer hormone replacement. There are also increasing case reports of pituitary deficiencies after repetitive sports injury [35–40]. This increased risk of hormonal sequelae from sports-related TBI has not yet been reflected in official guidance on sports-related concussions (from, e.g., the 2019 American Medical Society for Sports Medicine position statement on sports concussion, 2018 Association of Ringside Physicians consensus on combat sports concussion, or 2018 American Academy of Pediatrics statement sports-related concussions) [41–43].

Limited evidence suggests a similar increase in hormone dysfunction following blast injury as well as non-blast TBI incurred during military service. Several studies have examined pituitary hormone levels in US or UK military personnel who have sustained injury: one focused on mild blast-related TBI [44], one compared the effects of blast to non-blast moderate to severe TBI [45], and one compared hormonal profiles in service members deemed concussed vs non-concussed after being seen at a concussion center [46]. All results suggested higher rates of pituitary dysfunction after TBI during military service, but none of the study designs allowed for full pituitary evaluations. More recently, the results of complete pituitary evaluations of 58 veterans seen in a pituitary clinic in the US Veterans Administration system demonstrated high rates of both GHD (20.7%) and adrenal insufficiency (22.4%) [47•]. Veterans had symptoms associated with pituitary deficiencies and were evaluated at least 12 months after injury. This retrospective study included provocative testing, which was not possible in earlier studies relying on frozen serum samples.

Imaging and Biomarkers: Neither Imaging Findings nor Inflammatory Biomarkers are Clinically Useful Predictors of Pituitary Damage

Imaging is often readily available after TBI. Efforts to correlate brain imaging findings with pituitary function have not identified any consistent correlation. One study found isolated deficiencies [ACTH, thyroid stimulating hormone (TSH), or gonadotropins] to have a positive association with basal skull fracture and negative association with cranial vault fracture, and noted a correlation between pituitary deficiencies and diffuse axonal injury (diagnosed by CT in the context of delayed recovery) [48]; another study found no correlation between acute computed tomography (CT) imaging (1 week post-TBI in 71 patients) and pituitary hormones evaluated 2–3 years later [49].

Two study groups have found an association between anti-hypothalamus and anti-pituitary antibodies and pituitary dysfunction, in either the 1–6 months after TBI [50] or 5 years after TBI [51], but no clinically useful correlation has emerged. Tanriverdi and colleagues found anti-hypothalamus and anti-pituitary antibodies in, respectively, 60% and 48% of patients 5 years after TBI versus none in healthy controls [51]. While pituitary dysfunction was found more often in patients with strong anti-hypothalamus antibody positivity, the presence of anti-hypothalamus antibodies did not correlate with the development of pituitary dysfunction at 5 years. Vijapur and colleagues found elevated antibody levels in 143 men 1–6 months after moderate-severe TBI compared to 39 healthy controls, but found that men diagnosed

with persistent hypogonadal hypogonadism, defined as low testosterone with normal LH in half of samples 1–12 months post-TBI, had lower IgM levels [50].

Thus far, no clinically useful predictor has been identified. Even acute pituitary dysfunction—abnormal findings in the first months after injury—has been shown not to correlate with chronic pituitary deficiencies [3, 4, 9–11]. Persistent symptoms and signs consistent with pituitary deficiencies (discussed in the following section) should thus be used to determine whether pituitary hormone evaluation is indicated.

Pituitary Hormones and Their Role in Post-TBI Health

The pituitary sits within a bony saddle (sella) at the base of the skull, behind the sphenoid sinus. It is located below the hypothalamus, with which it regulates the growth hormone, reproductive hormone, thyroid hormone, and stress hormone systems, via an elegant feedback system.

The anterior pituitary produces growth hormone (GH), the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and prolactin. These hormones are central to hypothalamus-pituitary-end organ axes (Table 1), and their secretion is stimulated by the hypothalamus, with the exception of prolactin, which is tonically inhibited by hypothalamic signals. Pituitary hormone secretion also responds to end-organ hormone levels to maintain equilibrium, increasing when end-organ hormone levels fall or decreasing if end-organ hormone levels are too high. Understanding the feedback loops and diurnal variation of pituitary hormones allows interpretation of test results.

A potential pitfall in evaluation is illustrated in Fig. 1. TSH is often used as a screening test for thyroid hormone function. This only works in an intact system. If the pituitary gland is not functioning normally, as seen in central

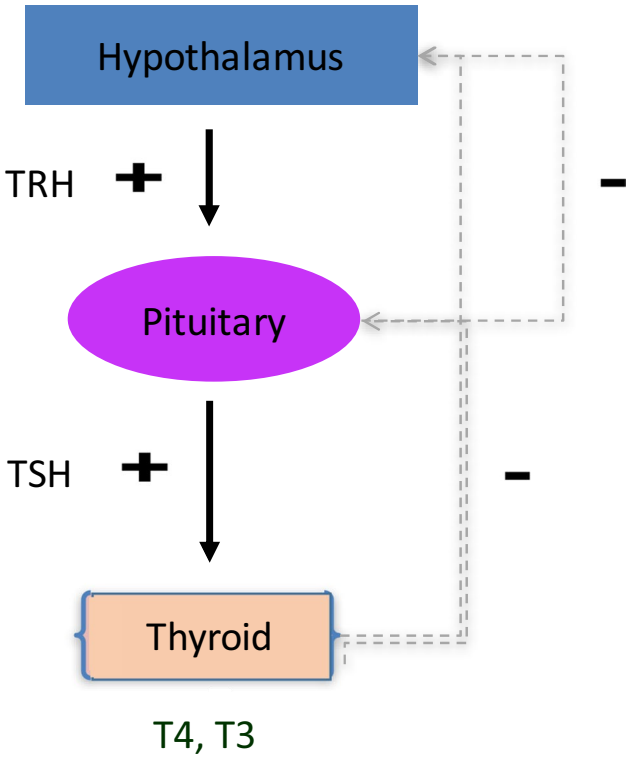

Fig. 1 Hypothalamic-pituitary-thyroid feedback loop. Thyrotropin-releasing hormone from the hypothalamus stimulates pituitary production of thyrotropin, or thyroid-stimulating hormone (TSH). TSH stimulates thyroid production of thyroid hormone (T4 and T3). If thyroid hormone production is too low, a feedback loop signals both hypothalamus and pituitary to increase TRH and TSH. Thus, elevated TSH is a sign of an underactive thyroid gland. Conversely, an overactive thyroid gland (or too much exogenous thyroid hormone) will suppress TSH secretion. TSH is often used as a screening test for thyroid hormone function. This only works in an intact system. If the pituitary gland is not functioning normally, as seen in central hypothyroidism, the pituitary is not able to mount a sufficient TSH response to the low levels of thyroid hormone caused by insufficient TSH. The TSH may be normal, but in the presence of low thyroid hormone levels, this is inappropriate. Thus, a normal TSH would be misleading. When pituitary dysfunction is suspected, both TSH and free (unbound) T4 should always be measured together

Table 1 Hypothalamic-pituitary-end organ hormones

Hypothalamic hormones	Pituitary hormones	End organ hormones
CRH	ACTH	Cortisol (adrenal glands)
TRH	TSH	Thyroxine (T4) and triiodothyronine (T3) (thyroid gland)
GnRH	FSH, LH	estradiol and ovulation (ovaries); spermatogenesis and testosterone (testes)
GHRH	GH	IGF-1 (liver)
	Prolactin	

Key: *ACTH* = adrenocorticotropic hormone; *CRH* = corticotrophin-releasing hormone; *FSH* = follicle-stimulating hormone; GH = growth hormone; *GHRH* = growth hormone-releasing hormone; *GnRH* = gonadotropin-releasing hormone; *IGF-1* = insulin-like growth factor 1; *TRH* = thyrotropin-releasing hormone; *TSH* = thyroid-stimulating hormone

hypothyroidism, the pituitary is not able to mount a sufficient TSH response to the low levels of thyroid hormone caused by insufficient TSH. The TSH may be normal, but in the presence of low thyroid hormone levels, this is inappropriate. Thus, a normal TSH would be misleading. When pituitary dysfunction is suspected, TSH should be measured together with free (unbound) T4.

Pituitary Hormones and Symptoms of Hypopituitarism

Pituitary deficiencies may have physical, cognitive, and emotional sequelae. While symptoms may be non-specific and overlap with other symptoms related to a TBI, it is helpful to recognize potential patterns associated with specific pituitary hormone deficiencies. Potential symptoms, initial evaluation, and replacement of anterior pituitary hormone deficiencies are described in Table 2.

Adrenal Insufficiency ACTH stimulates cortisol production from the adrenal glands. Cortisol (often termed "stress hormone") is essential in supporting the body during stress. Symptoms of adrenal insufficiency may appear as mild fatigue or nausea, or as severe exhaustion, weakness, weight loss, confusion, and hypotension. Extreme stressors may prompt adrenal crises, which may be fatal if untreated.

Hypothyroidism Pituitary TSH stimulates the release of thyroid hormone from the thyroid gland. Hypothyroidism due to a central deficit is symptomatically identical to primary hypothyroidism. Symptoms may include fatigue, weight gain, cold intolerance, constipation, menstrual irregularities, and changes to hair and skin. Children may display altered school performance.

Hypogonadism The pituitary hormones LH and FSH stimulate sex steroid synthesis and spermatogenesis/ovulation. Hypogonadal hypogonadism refers to low estrogen or testosterone due to hypothalamic or pituitary deficiency. Female hypogonadism may lead to menstrual irregularities, fatigue, mood changes, and an increased risk of osteoporosis and cardiovascular disease. Male hypogonadism may cause sexual side effects such as decreased libido, erectile dysfunction, and loss of spontaneous morning erections, and also depression, anemia, and decreased body hair and muscle mass. Children with hypogonadism will not undergo puberty without sex hormone replacement.

Growth Hormone Deficiency (GHD) Growth hormone (which leads to the production of insulin-like growth factor-1—IGF-1—in the liver) is important in both children and adults. Growth hormone is important in attaining intended adult height; effects of childhood GHD may include slowed height velocity and a cherub-like appearance due to altered fat distribution. Growth hormone has multiple important effects in adults. Growth hormone deficiency has negative effects on bones (low bone turnover), body composition (increased visceral fat, reduced lean mass), cardiovascular health, quality of life, energy, and exercise capacity, and there are increasing indications that sexual side effects are associated with GHD [52, 53]. Patients with GHD frequently describe "brain fog" and fatigue that impede activities of daily life.

Hyper-/Hypoprolactinemia Prolactin can be either increased or decreased as a result of TBI. Elevated prolactin levels may suppress the gonadal axis, and, at higher levels, lead to galactorrhea. Low prolactin levels may impede lactation.

Symptoms suggestive of pituitary dysfunction should prompt referral to a neuroendocrinologist for appropriate evaluation and management, as replacement of deficient hormones will ameliorate or reverse symptoms stemming from the hormone deficit.

Pituitary Hormone Replacement

The benefits of replacing deficient pituitary hormones are well established [54•]. Left untreated, anterior pituitary deficiencies are associated with decreased health and quality of life [55–59].

Pituitary hormone replacement improves physical, cognitive, and emotional symptoms. In addition to the many studies confirming the benefits of hormone replacement for deficiencies in the context of non-TBI etiologies such as pituitary adenomas, there are several studies in post-TBI populations. Studies of GH replacement in post-TBI GHD demonstrate benefits in quality of life [60•, 61] and cognition [62•], and there are case reports of improved physical parameters such as body composition [39, 63].

Pituitary hormones impact one another, making the order of evaluation and replacement important. Cortisol should be replaced first, followed by thyroid hormone, sex hormones, and then growth hormone:

cortisol → thyroid → testosterone/estradiol → GH

Issues, Trends, and Controversies

An overarching **issue** in this field is a lack of awareness that patients with even mild concussions are at an increased risk for pituitary hormone deficiencies [26•] and that these deficiencies can have lasting sequelae which may be reversible with hormone replacement. While neuroendocrine evaluation is straightforward, its use may be

Table 2 Evaluation and replacement of anterior pituitary hormone deficiencies

Pituitary hormone	End organ hormone	Potential symptoms (not exhaustive)	Potential initial evaluation	Replacement options[1]
ACTH	Cortisol	Fatigue, weakness, confusion, low sodium, hypotension	Early morning cortisol level; cosyntropin stimulation test	Glucocorticoid (prednisone or hydrocortisone are common examples)
TSH	Thyroid hormone	Fatigue, weight gain, cold intolerance, hair thinning, irregular menses, altered school performance	TSH, free T4 (simultaneous)	Levothyroxine
LH/FSH	Testosterone (male)	Fatigue, depression, anemia, loss of spontaneous morning erections, loss of libido, decreased body hair and muscle mass	LH, FSH, testosterone, and prolactin (simultaneous, in the early morning)	Testosterone (unless fertility is desired, in which case other hormones may be given)
	Estradiol (female)	Irregular menses, oligo/amenorrhea, mood changes, fatigue	LH, FSH, estradiol, and prolactin (simultaneous)	Estradiol (unless fertility is desired, in which case other hormones may be given)
GH	IGF-1	Fatigue, brain fog, impaired executive function, reduced exercise tolerance, changes to body composition	Provocative GH testing (glucagon stimulation, macimorelin, or insulin tolerance test in adults); IGF-1 sufficient if in the presence of 3 other deficiencies	Growth hormone
Prolactin (PRL)	–	Elevated PRL may suppress LH/FSH (leading to symptoms listed above) or cause galactorrhea PRL deficiency would be expected to impede lactation	PRL level	Elevated PRL that is symptomatic and not due to medication or other factors can be suppressed with dopamine agonists

Key: ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; PRL, prolactin; T4, thyroxine; TSH, thyroid-stimulating hormone

[1] Any hormone replacement should proceed under the care of a physician; replacement (or treatment of elevated prolactin) may not be appropriate in all cases

hampered by poor awareness of the potential sequelae and presentations of hypopituitarism. In addition, knowledge of appropriate evaluation for each hormonal axis—such as the use of free T4 with TSH to evaluate for central hypothyroidism, or the frequent necessity of provocative testing to evaluate for GHD (Table 2)—is not sufficiently widespread.

While the increased risk of pituitary hormone deficiencies following TBI is well described, and the benefits to appropriately replacing deficient hormones are clear, there remain unanswered questions. These include the exact incidence of hormonal deficiencies. The range in reported rates reflects differences in study designs, cohort features, and the manner in which pituitary hormones are evaluated; GHD in particular has a wide range of test methodology and diagnostic thresholds employed across studies, despite agreement among global guidelines [26•, 64–67] as to what constitutes deficiency. The specific mechanism by which TBI leads to pituitary deficiencies remains unknown. Proposed pathophysiologies include direct injury to the pituitary (or hypothalamus or infundibulum), neurovascular compromise, and the effects of secondary inflammation.

Suggestions that other forms of acquired brain injury also carry an increased risk of pituitary hormone deficiencies pose intriguing opportunities for additional research. There is some evidence that pituitary hormone dysfunction is seen at increased rates after subarachnoid hemorrhage and ischemic stroke, though definitions of deficiencies in this literature vary [39–43]. There are also suggestions that deficiencies in GH and other pituitary hormones may play a role in persistent post-acute sequelae of SARS CoV-2 infection, an area of current active research. Downregulation of genes involved in GH has been described in post-mortem studies of patients who died from COVID-19 [44], and a study of 43 patients 3 or more months following acute COVID-19 illness found definitive GHD in 20 patients (46.5%) [45]. We have recently described the case of a patient with lingering neurologic post-acute sequelae of COVID-19 (neuro-PASC symptoms) more than 1 year after COVID; he was found to have GHD, and symptoms have resolved on GHRT given as part of a clinical study.

Trends in this space include a focus on the effects of even mild TBI on symptomatic pituitary deficiencies, and increased attention to specific populations, including veterans who have suffered blast injury, adolescents and young adults exposed to repetitive sports injury, those in transition from adolescence to adulthood [68•], and women. There remains a high degree of interest in identifying predictive characteristics or biomarkers, and in better understanding whether pituitary deficiencies from TBI behave the same way as pituitary deficiencies from other causes: Should the same diagnostic thresholds be used? Is the effect of treatment the same? At present, recommended practice is to evaluate and replace post-TBI pituitary deficiencies as would be done with pituitary deficiencies from any other cause.

Current **controversies** in this field largely center around diagnosis and treatment of growth hormone deficiency. While there is general agreement that GHD should be evaluated and treated in patients with a history of TBI and symptoms consistent with GHD, practices differ as to when GHD evaluation and replacement is considered (Table 3). Many neuroendocrine centers delay testing of the GH axis until 12 months or more after injury, given that studies following subjects over one year have described recovery from GHD by 1 year, while others may test from > 3 months but delay replacement until 6–12 months after injury [26•]. My own practice has been to initiate GH axis testing as early as (but not prior to) 6 months after injury in patients who describe significant impact from symptoms associated with GHD, with the caveat that retesting is performed after 1 year on GH replacement (GHRT) to determine whether recovery has occurred. Further data regarding the natural history of pituitary deficiencies after TBI would offer important input.

Additional carefully designed studies will help elucidate unanswered questions, determining whom to screen, how and when to treat, and whether other mechanisms of acquired brain injury carry a similar risk to pituitary hormone axes.

Practical approach

While the increased rate of pituitary deficiencies after TBI is well-described, determining which patients to screen remains a challenge, and there are remaining questions regarding treatment initiation and duration. Differences in study design parameters and between guideline recommendations (Table 3) add to the challenge. In addition, symptoms of pituitary deficiencies and symptoms stemming from other aspects of TBI overlap, and the causal role of hypopituitarism in post-TBI symptoms will vary by individual and is difficult to predict prior to replacement. We offer here one practical approach to patients with a history of TBI and the potential for pituitary deficiencies.

In the acute period, adrenal insufficiency from alterations in the ACTH-cortisol axis is important to consider, but there is no known role for evaluating the other anterior pituitary axes; measured changes may serve a compensatory purpose. Posterior pituitary hormones may also be affected in the acute period, leading to DI and/or SIADH, which are most often transient.

In patients with a history of TBI, persistent symptoms or signs suggestive of pituitary hormone deficiencies should prompt evaluation, given the reported incidence and the potential sequelae of deficiencies. Untreated anterior pituitary deficiencies lead to worsened health and quality of life,

Table 3 Guidelines and recommendations for post-TBI pituitary hormone management.

Paper	ACTH	TSH	LH/FSH	GH	Screening criteria (chronic)
2005 Consensus guidelines on screening for hypopituitarism following TBI (Ghigo et al. 2005) [25]	Test and replace in the acute period	Test and replace in the acute period in the presence of AI or DI; otherwise, at 3 and 12 months	Test and replace in the acute period in the presence of AI or DI, and otherwise at 3 and 12 months Retest prior to initiating replacement	Test and replace acutely if AI or DI is present, and otherwise at 3 and 12 months (after replacing other deficiencies) Retest prior to GH replacement, delaying replacement to 12 months if isolated GHD	All patients after TBI, at 3 and 12 months, or at presentation in the absence of prior evaluation
2007 Consensus guidelines for the diagnosis and treatment of adults with GH deficiency (Ho et al.2007) [64]				> 12 mos	GH evaluation at > 12 months after TBI
2012 study on outcomes of male hypogonadism after severe TBI (Wagner et al. 2012) [2]			12–16 weeks		-
2015 AACE neuroendocrine approach to patients with TBI (Tritos et al.2015) [8]	In the acute period and at > 3 months	After acute illness, > 4 weeks out	Stable outpatient	After several months	At several months after either moderate-severe TBI, or mild TBI[1] in the presence of symptoms and impaired QOL
2017 British Neurotrauma Group guidance on the screening and management of pituitary dysfunction following TBI in adults (Tan et al.2017)[6]	No acute testing; treat empirically if clinically warranted Test at 3–6 months	3–6 months	3–6 months	> 12 months	At 3–6 months if history of > 48-h hospitalization, or persistent symptoms
2020 review of the Long-term neuroendocrine consequences of traumatic brain injury and strategies for management (Hacioglu et al. 2020) [71]		6 mos	6 mos	> 12 mos	All patients at 6 and 12 months Annually up to 5y only if mild complicated TBI No testing after 12 months if moderate-severe TBI
2022 consensus on care in patients with growth hormone deficiency and mild traumatic brain injury (Yuen et al. 2022) [26•]	> 3 months (does not address acute period)	> 3 months	> 3 months	6–12 months	Measure axes at > 3 months; GHD replacement after > 6–12 months

Updated and adapted from Wexler TL, Neuroendocrine Dysfunction After Traumatic Brain Injury. In Zasler ND, Katz DI, Zafonte RD, Brain Injury Medicine, Third Edition (chapter 54). 2021. New York, NY: Demos Medical Publishing, Springer Publishing Company

[1]AACE's 2019 guidelines, addressing GHD in the transition from pediatric to adult care, recommend that GHD be evaluated only 12 months after TBI due to the potential for recovery [67]

AACE, American Association of Clinical Endocrinologists; *AI*, adrenal insufficiency; *DI*, (central) diabetes insipidus, also arginine vasopressin deficiency; *FSH*, follicle-stimulating hormone; *GH*, growth hormone; *GHD*, growth hormone deficiency; *LH*, luteinizing hormone; *QOL*, quality of life; *TBI*, traumatic brain injury; *TSH*, thyroid-stimulating hormone

and have been associated with increased mortality as well as morbidity [55–59]. Referral to neuroendocrinology is recommended in the presence of persistent symptoms such as irregular menses, decreased libido or frequency of spontaneous morning erections, fatigue, and "brain fog" or subjective executive function decrements, and new changes to weight, skin, or hair.

Screening laboratory tests may be useful, but it is important to note that any possibility of adrenal insufficiency requires prompt follow-up given that it is the one anterior deficiency that may be fatal if not appropriately treated. Laboratory values which may be useful for endocrine interpretation include early morning cortisol, TSH and free T4, LH/FSH/prolactin with testosterone or estradiol (unless the patient has normal menses or is on hormone replacement), and IGF-1. Certain axes cannot be interpreted if other hormones are deficient. Diagnosis of male hypogonadism requires several low morning testosterone values in the presence of symptoms and thus cannot be diagnosed by a single set of laboratory results. Evaluation for growth hormone deficiency often requires GH stimulation; while IGF-1 was used as a screening test for years, it is now clear that patients with normal IGF-1 levels can be diagnosed as having GHD on provocative testing [11, 69, 70].

Replacement of established pituitary hormone deficiencies is recommended. Replacement should proceed in order, with adrenal insufficiency always addressed promptly and first; providing thyroid hormone replacement may precipitate adrenal crisis in patients with unrecognized adrenal insufficiency.

Symptoms due to pituitary deficiencies should be alleviated or reversed by replacement. It is helpful to set expectations appropriately, noting that, unless all symptoms are entirely due to pituitary deficiencies, a return to overall baseline is not expected. Evaluations may need to be repeated, particularly if replacement is initiated within the first year or if symptoms change.

Given the negative health effects of untreated hormone deficiencies and the opportunity to alleviate or reverse chronic and debilitating symptoms with hormone replacement, it is important to raise awareness of the increased rate of pituitary hormone deficiencies after TBI.

Conclusions

The increased risk of pituitary hormone deficiencies following traumatic brain injury is well-described. These deficiencies may appear at a delay and after even mild TBI. However, there remains insufficient awareness of the role that hypopituitarism may play in post-TBI emotional, cognitive, and physical health. Recognition of the presentation of pituitary hormone deficiencies, and appropriate evaluation and replacement, will promote identification of a reversible component to post-TBI health and recovery. There is growing evidence that pituitary deficiencies may also play a role in health after specific types of traumatic injury (such as military blast injury), and after other types of acquired injury (subarachnoid hemorrhage, ischemic stroke, neuro-PASC). There is ample opportunity for additional research into the role that hypopituitarism may play in not only TBI but other acquired brain injuries as well.

Declarations

Conflict of interest Tamara Wexler served on scientific advisory boards for Novo Nordisk and Sandoz in 2020, on the topic of traumatic brain injury.

Human and Animal Rights and Informed Consent Tamara Wexler served on scientific advisory boards for Novo Nordisk and Sandoz in 2020, on the topic of traumatic brain injury.

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