Posttraumatic Hypopituitarism: Neuroendocrine Dysfunction and Treatment

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Introduction

Traumatic brain injury (TBI) contributes to a substantial number of deaths and cases of permanent disability in the United States annually. Life-long consequences of sustaining a TBI can include impairments in physical, cognitive, and psychosocial functioning [1]. The Center for Disease Control (CDC) estimates that at least 5.3 million Americans, ~2% of the United States population, are dependent on the care of another person to perform activities of daily living as a result of TBI [2]. Brain injury severity (typically assessed by alternation of or duration of loss of consciousness [LOC] and posttraumatic amnesia [PTA], as well as Glasgow Coma Scale [GCS]) is associated with the development of cognitive deficits and personality/behavioral changes in the acute period [3]. Moderate-to-severe TBI can result in significant loss of function in the areas of motor skills, communication skills, sensation, emotional stability, psychosocial adjustment, and a range of cognitive parameters that can render an individual unable to function in society at premorbid levels of functioning in the postacute period [4]. LOC is not considered a reliable predictor of future outcomes post-TBI and is measured as follows: <30 minutes = mild; 30 minutes–24 hours = moderate; >24 hours = severe. PTA (i.e., <1 day = mild; 1–7 days = moderate; >7 days = severe) is the period of time from injury onset to the return of continuous day-to-day memories, and is typically viewed as a more robust predictor of length of hospitalization, recovery rates, and functional outcome [5, 6]. Patients experiencing PTA can display heightened levels of aggression and agitation including disorientation, impulsive behaviors, irritability, confabulatory responding, amnesia (retrograde and anterograde), and impaired attentional skills that may be initiated or prolonged by overstimulating environmental factors [7]. Another measure of TBI severity is the 15-point GCS, which includes an assessment of the patient's level of consciousness, orientation, and motor initiation. GCS scores of 13–15, 9–12, and 3–8 indicate mild, moderate, and severe levels of TBI, respectively [3]. The GCS score is typically viewed as a rough estimate of TBI severity, because the designation of coma can be influenced by many factors [8].

Pituitary dysfunction following TBI was initially reported early in the twentieth century [9];

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however, the possibility that acute TBI can result in pituitary dysfunction has only recently been appreciated [10–12]. Approximately two-thirds of individuals who have come to autopsy following TBI have been found to have structural abnormalities of the pituitary, pituitary stalk, and/or hypothalamus [13]. Hence, the hormones produced by the pituitary gland or regulated by the pituitary axis may be negatively impacted by TBI. Chronic dysfunction of the pituitary axis is observed in approximately 35% of individuals who sustain a moderate-to-severe TBI. The most common deficiency is that of growth hormone (GH), followed by gonadotropin, cortisol, and thyroid hormones (T3 and T4) [14]. Previous work has demonstrated that hypopituitarism, particularly growth hormone deficiency (GHD), is common among survivors of TBI [15]. The prevalence of GHD in patients with TBI varies within the range 10–25% [11]. GHD is associated with multiple physical, metabolic, and neuropsychological manifestations, including, but not limited to, diminished lean body mass, disrupted lipoprotein and carbohydrate metabolism, reduced bone mineral density, and impaired cardiac function, as well as declines in cognitive functioning, fatigue, and diminished quality of life (QoL) [16, 17]. Therefore, providing appropriate diagnosis of GHD in patients with the aforementioned symptoms is crucial, as subsequent management using GH replacement therapy has been shown to improve cognitive, psychiatric, and physical symptoms [17–21].

The purpose of this chapter is to provide an update of the literature with regard to posttraumatic hypopituitarism (PTH) and to relate these findings to neuroendocrine dysfunction and symptom detection and management. While PTH can result in multiple neuroendocrine abnormalities, it has become clear that GHD is most common. Findings from recent studies indicate that, in a significant proportion of patients with moderate-to-severe TBI, observed cognitive, psychiatric, and physical/functioning sequelae may be attributed, in part, to GHD with a good potential for symptom improvement following GH replacement. It is our view that moderate-to-severe TBI is a chronic disease process and the physical/functioning, cognitive, and psychiatric consequences of untreated endocrinopathies are extensive and detrimental to functional outcomes.

Posttraumatic Hypopituitarism (PTH)

The adult pituitary gland is a pea-sized structure (approximately 600 mg in weight) and lies beneath the brain in the middle cranial fossa. The pituitary gland sits within a bony cave called the sella turcica and is connected to the hypothalamus by the pituitary stalk. The superior hypophyseal arteries branch from the internal carotid artery to supply the hypothalamus. The long and short hypophyseal vessels (which form the hypothalamic portal circulation) provide the blood supply to the pituitary gland. Severed portal vessels are capable of regeneration and, therefore, permit some resumption of anterior pituitary function post injury, although this process is likely to be quite slow and not always complete [22]. Following trauma to the head, the vascular supply to the pituitary gland is tenuous, but confinement of the pituitary within the sella turcica by the diaphragma sella renders the infundibulum and stalk vulnerable to shearing. As cortical swelling is limited by the skull following brain injury, pituitary gland is also swelling, limited by its bony encasement. Pituitary gland compression will include that of the long portal vessels between the stalk and the free edge of the diaphragma sella. The fragile vessels are also susceptible to pituitary stalk rupture or transection as well as vasospasm and hypotension [8].

The structurally larger part of the pituitary, the anterior lobe, is more glandular than neuronal in appearance. Neural cells within the hypothalamus synthesize specific inhibiting and releasing hormones, which are secreted directly into the portal vessels within the pituitary stalk. The portal vessels then carry these hormones to the secretory cells within the anterior lobe. The somatotrophs, responsible for the secretion of GH, constitute approximately 40% of pituitary cells. The corticotrophs,

responsible for adrenocorticotropic hormone (ACTH), constitute approximately 20% of the anterior pituitary cells. The thyrotrophs, which secrete thyroid stimulating hormone (TSH), constitute 5% of the anterior pituitary cells, and are located in the anterior medial region of the gland. The gonadotrophs secrete follicle-stimulating hormone (FSH) and leutinizing hormone (LH) and constitute 10–15% of the anterior pituitary cells [23]. Prior work has suggested that the most common hormonal dysfunction following PTH is GHD resulting from somatotrophic cell death due to impaired blood and oxygen supply [12, 24]. The least common pituitary abnormality noted post TBI is TSH deficiency [25].

The most probable mechanisms of PTH are (1) primary physical effects of brain damage, (2) indirect injuries, such as hypoxia or hypotension, and/or (3) the transient effects of critical illness and medication. Direct mechanisms refer to fractures through the skull base and sella turcica, as well as the shearing injuries of the pituitary, infundibulum, and/or hypothalamus. Transection or rupture of the pituitary stalk results in anterior pituitary lobe infarction because of disruption of the portal blood supply from the hypothalamus to this region. Indirectly, functional damage at the hypothalamic–pituitary region can be the result of a secondary hypoxic insult. Another possible means of damage is diffuse axonal injury (DAI) caused by acceleration–deceleration along with rotational forces, common in motor vehicle crashes [14].

PTH has been associated with adverse effects in patients in the acute or chronic stages, including reduced QoL and rehabilitation outcomes with direct adverse effects on health outcomes including ischemic heart disease and increased mortality [8, 26–32]. It is important to mention that hypopituitarism can present without TBI. The incidence of idiopathic clinically apparent hypothyroidism is approximately 2% in adults and is 10-times more common in females than males [33]. The incidence, however, of subclinical or asymptomatic GHD, hypogonadism, or hypocortisolism is unknown. Although it is certainly possible that an individual with PTH may have had pre-existing asymptomatic hypopituitarism (especially hypothyroidism), the numbers most likely would be very small, as deficiencies in these other axes would be clinically apparent.

Neuroendocrine Dysfunction: Prevalence, Symptom Detection, and Hormone Screening

Determining a "true" prevalence for neuroendocrine dysfunction following TBI has been difficult due to methodological differences between studies, including timing of hormone assessments post-TBI, injury severity, age of onset, types of hormones studied, and the methods used to diagnose pituitary hormone dysfunction. Hence, these factors need to be taken into account when comparing across studies. Prevalence of anterior hypopituitarism in the chronic phase of TBI varies, ranging from 15% to 50% with GHD prevalence ranging from 6% to 33% in the chronic phase of recovery [11, 12, 34–43].

Aimaretti and associates examined pituitary hormone levels in patients with mild, moderate, and severe levels of TBI at 3 months and 12 months post injury [35]. PTH was found in 33% of patients at 3 months and 23% of patients at 1 year. Seventy-five percent of the patients with single or multiple axis abnormalities at 3 months had reverted to normal at 12 months. Conversely, 6% of patients who had normal pituitary hormone levels at baseline developed single-axis PTH at 1 year, and 13% who had single-axis deficiencies at 3 months had developed multiple deficiencies at 1 year. Interestingly, of the 32 patients with a GCS score of 13 or greater at time of injury (i.e., mild), 13 (41%) had chronic pituitary deficiencies, suggesting that the incidence of PTH in mild TBI (mTBI) is considerable. Similarly, Benvenga and associates reported a case series of more than 300 patients with pituitary dysfunction secondary to TBI [10]. Hormonal abnormality was common in their sample, with indications that such abnormalities can readily occur in those individuals with mTBI. Krahulik and associates followed 89 patients with PTH over time and discovered that 21% had developed hormonal dysfunction [44].

Deficits in the somatotropin axis were most common, followed by hypogonadism. As with the Aimaretti and coauthors study noted above, Krahulik and coauthors also observed patients who recovered their normal axis function over time and also found patients who were normal at the time of injury or at 3 months postinjury who subsequently developed PTH [44]. Schneider and coauthors reviewed the prevalence of PTH in 825 patients at least 5 months post injury in a multicenter study performed in Austria and Germany [45]. They discovered at least one hormonal abnormality in 38% of patients. The prevalence of PTH in individuals with mild, moderate, and severe TBI was 17%, 11%, and 35%, respectively, again demonstrating that individuals with less severe injuries are still at risk for developing hormonal deficiencies. In a similar vein, repetitive head trauma from sport-related injuries has become an area of great interest, especially over the past decade. There have been small studies showing a relationship of repetitive head trauma and PTH, including a case report of an adolescent with at least four sport-related concussions who complained of fatigue and was found to have multiple pituitary deficiencies [46, 47]. Further, Kelly and coauthors discovered PTH in 24% of 68 retired profootball athletes [48]. These studies clearly suggest that early pituitary deficits may recover over time, and that, conversely, normal pituitary function early after injury may become abnormal at 3–12 months. Recovery does not appear to occur in those patients who develop deficiencies of all pituitary hormones (i.e., panhypopituitarism).

As described above, hypopituitarism can be one of the immediate consequences of TBI, with some hormone deficiencies resolving over time, while others emerge. However, approximately 6 months post TBI, hormone deficits appear to be stable and relatively permanent [49]. Due to the fluctuations in hormone levels following TBI, consensus guidelines from the American Association of Clinical Endocrinologists and American College of Endocrinologists have recommended that all patients with moderate-to-severe TBI be assessed for neuroendocrine dysfunction during the acute and chronic phases of their recovery and patients with mTBI who are experiencing symptoms should be offered hormone assessment [24, 50–52]. An algorithm for the timing of a baseline hormone workup has been proposed by Ghigo and coauthors and is as follows: For all TBI patients, regardless of severity, hormone assessments should be conducted during hospitalization and if hyponatremia and hypotension are present [24]. Assessments should be repeated at 3 and 12 months after any severity of TBI. Retrospectively, if patients with TBI have any signs or symptoms of hormone dysfunction and are at least 12 months post-TBI, immediate hormone testing should be conducted, as it is unlikely that any hormone deficiencies are transient at this point [24].

Patients with moderate-to-severe TBI typically have deficits that require medical evaluation and/or intervention, which would allow patients with this level of injury severity an opportunity to have symptoms examined and potentially be evaluated for neuroendocrine dysfunction. However, patients with mTBI typically do not present to an emergency room or physician until many months post-TBI. At this point, the symptoms of TBI are often labeled as "postconcussion syndrome" and alternative explanations for persisting symptoms may not be readily explored. As discussed above, neuroendocrine dysfunction can occur with all severity levels of TBI; however, it has been primarily investigated in patients with moderate-to-severe TBI. Schneider and coworkers published a systematic review of hypopituitarism following TBI in which they attempted to determine the prevalence of hypopituitarism by injury severity [32]. Studies were reviewed that included all TBI severities [35, 36, 42, 43], only moderate-to-severe TBI [34, 41], and only severe TBI [37, 40]. Results from these studies were inconsistent, as some reported no relationship between hypopituitarism and severity of TBI [34, 35, 37, 41–43], while others reported more frequent rates of hypopituitarism in patients with more severe TBI [36, 38]. All studies that had included all severities of TBI in the chronic phase of recovery were further analyzed, and results from the pooled prevalence of hypopituitarism revealed that the frequency of hypopituitarism was greater in severe TBI (35.3%; 95% CI = 27.3–44.2%) than in moderate

(10.9%; 95% CI = 5.1–21.8%) and mTBI (16.8%; 95% CI = 10.9–25.0%). Future studies are needed to investigate prevalence of specific hormone deficiencies by injury severity.

Despite clear evidence that a large number of survivors of TBI can experience hypopituitarism, few patients are routinely screened as part of their routine clinical workup for TBI. This could be due, in part, to the considerable overlap of symptoms between TBI and hypopituitarism. Symptoms such as memory and concentration impairments, decreased intelligence quotient (IQ), decreased QoL, fatigue, anxiety, depression, social isolation, deterioration in sex life, and increased unemployment, which are frequently reported in patients with TBI, have also been reported in patients with adult-onset GHD and no documented brain injury [11, 24]. These symptoms also tend to be nonspecific to hypopituitarism and could be attributed to many different disorders, including depression, chronic fatigue syndrome, and postconcussion syndrome.

Proper screening and evaluation of pituitary hormones following TBI is essential to definitively diagnose hypopituitarism and potentially treat the underlying cause of these symptoms. Routine basal hormone screening involves assessing each individual axis of the pituitary separately. Serum levels of TSH and free T4 (thyroxine) should be measured to evaluate the thyroid axis. A diagnosis of central hypothyroidism can be made with a normal or low TSH and low levels of free T4 [53, 54]. The gonadal axis is assessed by measuring baseline levels of FSH and LH, along with free and total testosterone levels in men and an estradiol level in premenopausal women who are not menstruating regularly. Central hypogonadism can be diagnosed with low levels of testosterone or estrogens with either normal or low FSH and LH levels [30, 37, 41]. Prolactin levels should also be measured in both sexes as increased levels can indicate underlying structural pathology of the pituitary [53, 55]. Basal hormone levels for the thyroid, gonadal, and prolactin axes are sufficient for a diagnosis [35, 37, 47]. However, adrenal insufficiency and GHD require provocative testing in addition to basal hormone screenings. Adrenal insufficiency can be initially screened by a basal morning cortisol level. If cortisol levels are less than 500 nmol/L, a referral to an endocrinologist is warranted for further assessment, including a dynamic stimulation test to assess adrenal reserve [11].

Insulin-like growth factor-1 (IGF-1) is often used as a surrogate marker of GH levels and is included as part of basal hormone screenings [21, 24, 51]. Reliance on IGF-1 as an assessment of GH function after TBI is standard practice, but its use needs to be re-evaluated, because 50% of adults with GHD have IGF-1 levels within the normal reference range [56]. Similarly, patients with a normal GH response can have low IGF-1 levels [24, 39]. Direct serum assessment is unreliable because of the pulsatile release of GH and results in serum fluctuations within a 24-hour period [57]. Thus, provocative testing is essential to definitively diagnose GHD [24, 51]. Peak GH secretion during provocative testing is used to assess the capacity of the pituitary to release GH [21]. The insulin tolerance test (ITT) is considered the "gold standard" in provocative tests for diagnosing GHD [24, 58, 59]; however, it cannot be safely performed in patients with seizures or severe cardiovascular disease [60, 61]. This contraindication limits its use in patients with TBI. The glucagon stimulation test (GST) has comparable diagnostic accuracy and reliability as the ITT [62] and is well tolerated in patients with TBI [51, 63]. A single provocative test is sufficient for the diagnosis of GHD in adults [64]. It should be noted that basal hormone assessments and the results of provocative tests need to be interpreted within the context of the patient's medical history, clinical exam, and symptoms.

Cognitive, Psychiatric, and Physical/Functioning Sequelae

Cognitive Dysfunction

Regions of the brain that are particularly vulnerable to TBI include the frontal lobe, anterior temporal lobe, corpus callosum, brainstem, and limbic structures, such as the basal ganglia and hypothalamus [65]. Consequently, cognitive and behavioral processes commonly disrupted by

TBI include arousal, attention, speed of information processing, new learning, memory retrieval, fluency, and executive functions (including organization and planning, sequencing, multitasking, judgment, and abstraction) [66, 67]. While the specific neuropsychological impact of PTH remains unclear, GHD due to PTH is associated with changes in body composition, as well as impaired QoL, cognitive disturbance, and psychological sequelae [68]. It is important to mention that the impact of hypopituitarism, particularly GHD, on cognition from causes other than TBI has been studied in children and adults. Both have been associated with cognitive impairments in memory, attention/concentration, and information processing speed [69–75].

Wamstad and coworkers did not report significant group differences on tasks of cognition in children and adolescents with (n = 9) or without (n = 18) GHD (based on provocative testing) following moderate-to-severe TBI [76]. Kelly and coworkers failed to find significant differences in patients who were GHD post TBI on tasks that assess memory and attention/concentration compared to those who were GH-sufficient post TBI [77]. However, compared to patients with normal pituitary function, those with deficits in the GH axis had higher rates of at least one marker of depression, as well as reduced QoL in the domains of physical health, general health, emotional health, pain, energy, and fatigue. Popovic and coworkers assessed the relationship between GHD and cognitive disabilities and mental distress in 67 patients with moderate-to-severe TBI [41]. They discovered a significant relationship with peak GH levels to short- and long-term memory deficits, paranoid ideation, and somatization, as well as an association between lower IGF-1 levels and impaired visual memory. In their study, Leon-Carrion and coworkers were able to demonstrate cognitive impairment in patients with TBI and GHD on neuropsychological tasks that assess attention, executive functioning, and memory compared to patients with TBI who were GH-sufficient [78]. The GHD group demonstrated greater deficits in simple attention, memory (increased errors in intrusion and repetition), increased reaction time, and greater emotional disruption. The results were interpreted as supporting the concept that some deficits post TBI may be the direct result of GHD, rather than being attributable more generally to the brain injury per se.

The mechanism underlying the effects of GH on cognition is not entirely understood. GH receptors are located throughout the brain. From the animal literature, it is clear that GH and IGF-1 play a role in modulating the N-methyl-D-aspartate (NMDA) receptor. GH influences the NMDA receptor system in the hippocampus, an essential component of long-term potentiation (LTP), which is highly involved in memory acquisition [79, 80]. Furthermore, there may be a relationship between the NMDA receptor subunit mRNA (messenger ribonucleic acid) expression levels and learning ability. Learning is improved by GH replacement in rats that have had their pituitaries removed [79]. Additionally, following central nervous system injury in humans, IGF-1 has also been found to increase progenitor cell proliferation and numbers of new neurons, oligodendrocytes, and blood vessels in the dentate gyrus of the hippocampus [81]. In contrast, deficiency in GH and IGF-1 decreases survival of dentate granule neurons within the hippocampus [82]. Devesa and associates posited that treatment with GH in patients with PTH may increase the number of newly formed neurons in the hippocampal dentate gyrus, a zone related to recent memory [83].

Psychiatric Symptomatology

Psychiatric symptoms and maladaptive behaviors (e.g., depression and/or behavioral disinhibition) experienced by patients with TBI can be a significant limiting factor for rehabilitation participation and positive functional outcomes [5, 31, 84, 85]. Depression is common following TBI, with prevalence rates estimated to be 30–38% [86]. Given the lifetime prevalence of depression in the United States, which has been reported to be 16.2%, there appears to be an increased risk of developing depression after TBI over and above one's lifetime risk [87]. However, in a cross-sequential analysis, Ashman

and associates found that rates of depression following TBI can decline with time since injury [88]. Many factors coincide with TBI, including pain, fatigue, sleep disturbance, cognitive dysfunction, apathy, decreased mobility, and emotional processing deficits, that can result in the experience of depression by themselves or may have a cumulative effect with a resulting increase in depression risk post TBI [89]. Depression in individuals with TBI can also be the result of a reaction to the injury itself and/or result from other psychological changes; however, emotional and behavioral sequelae can also be the direct result of specific neurotransmitter and/or neuroendocrine system dysfunction [90, 91].

The monoamine deficiency hypothesis purporting that decreased levels of serotonin, norepinephrine, and γ-aminobutyric acid (GABA) result in depression is one theory applied to the experience of depression post TBI [92]. Disruptions of serotonin, glutamate, and dopamine levels have been identified in TBI patients [91]. Another theory is that of dysregulation of the hypothalamic–pituitary–adrenal axis (HPA axis) by physical or emotional stress. Both overactivation and underactivation of the HPA axis have been reported in TBI [55]. This theory posits that the amygdala and hippocampus, structures that regulate emotions and memory, have connections to the hypothalamus and are ultimately affected by neuroendocrine imbalance post injury [93]. Stress-induced cortisol released by the adrenal cortex appears to play a role in depression and is characterized by a more chronic course of depression, hippocampal atrophy, and reduced levels of brain-derived neurotrophic factor [94].

Fatigue and Physical/Functioning Impairment

Fatigue, not to be confused with depression, is typically viewed as a subjective phenomenon that can be expressed, for example, as experiencing a lack of energy or motivation, weakness, and/or sleepiness and has been reported to greatly impact patients' lifestyles by limiting participation in therapeutic, social, and/or leisure activities [95–97]. The association between depressed mood and fatigue post TBI is not entirely clear. The consensus from prior work indicates a consistent, but not necessarily causative, association between subjective fatigue and psychiatric disorder (e.g., depression) in this patient population [98, 99]. In their study assessing potential correlates of fatigue in patients with TBI, Ponsford and coworkers discovered that patients with symptoms related to depression were more likely to report significant levels of fatigue; however, so were patients who also experienced heightened levels of pain and cognitive dysfunction [100]. Zgaljardic and associates have proposed a mechanism of TBI-related fatigue (Fig. 1) [99]. They posited that, as TBI can result in neuropsychological impairment, pain, sleep disorders, and, in some individuals, endocrine dysfunction, the injury can elicit inflammation and oxidative stress initially at injury foci and, later, possibly in additional tissues through indirect effects, such as TBI-induced physical inactivity or mitochondrial impairment secondary to hormone deficiencies, including GH. Mitochondrial and cardiovascular dysfunction, as well as oxidative stress, may contribute to peripheral fatigue (i.e., impaired muscle performance secondary to exertion). Notably, central fatigue-induced (i.e., from a neuropsychological standpoint, a subjective view of one's fatigue symptoms) reductions in physical activity may initiate a self-reinforcing cycle of both central fatigue and peripheral fatigue.

While several factors appear to contribute to symptoms related to fatigue post TBI, GHD warrants specific consideration, as GHD in the absence of TBI is associated with fatigue [101–104]. Thomas and associates reported reduced aerobic capacity in patients with GHD but without TBI that are similar in magnitude to those observed in patients with TBI and GHD [105]. GHD has also been reported in a subset of patients with fibromyalgia, a group in which fatigue is a cardinal characteristic [106–110]. GHD may have a direct impact on skeletal muscle mitochondrial function, as GH stimulates

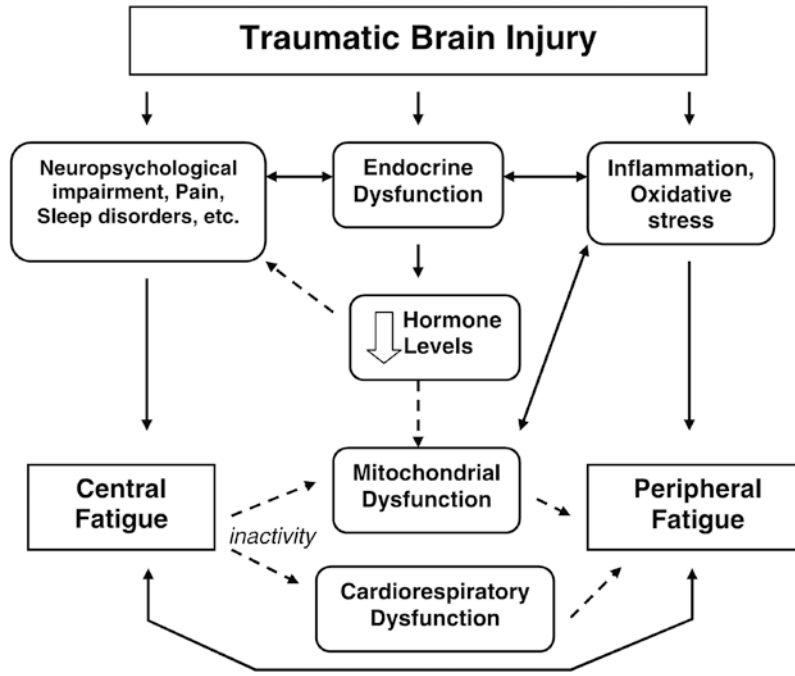

Fig. 1 Proposed mechanism of TBI-related central and peripheral fatigue. (Used with permission of Taylor & Francis from Zgaljardic et al. [99])

skeletal muscle mitochondrial enzyme activity and adenosine triphosphate (ATP) synthesis [111, 112]. Impaired skeletal muscle mitochondrial function may, thus, be partially responsible for the reduced maximal aerobic capacity in individuals with GHD but without TBI [104]. In patients with both TBI and GHD, VO_{2max} (maximum rate of oxygen consumption) is considerably worse relative to patients with TBI and adequate GH levels, which could reflect further impairment of skeletal muscle mitochondrial function [113]. These findings suggest that GH replacement may improve cardiorespiratory capacity in TBI patients with GHD (peak GH level less than 3 ng/mL) and GH insufficiency (peak GH response between 3 and 10 ng/mL).

PTH has been associated with significant negative consequences in physical/functioning. Clinical symptoms associated with hypopituitarism are dependent on the specific hormone axis affected, severity of the hormone deficiency, gender, and whether the deficiency is acute or chronic. Physical symptoms may be nonspecific, such as fatigue, changes in weight, and hypotension, and, as such, are often attributed to the brain injury and not linked to a hormone deficiency. The effects of hormone deficiency may potentially impede progress in rehabilitation, impair recovery, and may even contribute to significant morbidity following TBI [19, 34, 114, 115]. Hormone deficiencies can negatively influence recovery from brain injury, even if the patient is undergoing intense rehabilitation [116, 117]. Understanding the signs and symptoms of hormone deficiency may assist in the timely diagnosis and treatment of hypopituitarism following TBI.

Clinical manifestations of glucocorticoid deficiency can include fatigue, pallor, myopathy, anorexia/weight loss, weakness, hypotension, nausea, and hypoglycemia [32]. These symptoms can be life-threatening and require hydrocortisone therapy as soon as the diagnosis can be confirmed by an ACTH stimulation test [8]. Some of the symptoms of a glucocorticoid deficiency overlap with those of a thyroid deficiency, specifically fatigue and myopathy. Other clinical indicators of thyroid deficiency include cold intolerance, constipation, weight gain, hair loss, dry skin, bradycardia, hoarseness, and slow mental processing [32, 34]. Thyroid hormone replacement typically begins after serum cortisol levels are within normal limits [8].

Hypogonadism has been associated with adverse effects on reproductive functioning, including infertility, decreased libido, and impaired sexual function. Clinical symptoms of hypogonadism specific to women include amenorrhea, osteoporosis, and premature atherosclerosis. Testosterone deficiency in men is associated with decreased muscle and bone mass, erythropoiesis, hair growth, decreased energy, and impaired exercise tolerance [116]. If left untreated, hypogonadism can cause premature mortality secondary to cardiovascular disease [118]. Improvements in sexual function, libido, and muscle and bone formation have been reported with testosterone replacement in men [119, 120], and estrogen replacement has been associated with improved cognitive functioning in women [121, 122].

Untreated adult-onset GHD presents clinically as abnormal body composition, specifically decreased muscle mass [123], altered bone metabolism [124], and greater body fat [38, 125] in conjunction with decreased exercise capacity [113, 126], fatigue [125], low energy [77, 127], increased insulin resistance [125], unfavorable lipid profile [38], and decreased QoL [128]. Due to its adverse effects on metabolism and cardiovascular function [129], GHD may increase the risk of mortality [30, 118, 130, 131]. After GHD has been diagnosed, GH replacement is warranted. GH replacement in adults without TBI has been shown to improve body composition through decreased waist circumference [125], increased muscle mass [132], improved metabolic profiles [125], and improved cardiac function [133].

TBI as a Chronic Disease: GH Replacement Therapy

As more is learned about PTH, the previously held concept that trauma induced physical impairment of the pituitary, resulting in hormone deficiency, is beginning to change. The new concept is centered on the hypothesis that a percentage of the population is at risk to develop a chronic disease process, most likely inflammatory, in the brain after trauma of varying degree. Much like any chronic disease, the manifestations of this chronic disease can vary across a spectrum of signs and symptoms as can the severity of the presentation. Therefore, pituitary dysfunction is one of the manifestations of the chronic disease process, and GH is the most common hormone affected.

This concept is supported by several studies that show a benefit with GH replacement in patients with abnormal GH secretion by stimulation testing, but without a classical diagnosis of GHD [9, 113]. As mentioned above, a stimulation test is used to diagnose GHD, since GH is secreted from the pituitary in sporadic bursts, and many times GH blood levels are undetectable. Glucagon given intramuscularly (i.e., GST) will stimulate GH release as will insulin-induced hypoglycemia (i.e., ITT). A response of GH of less than 3 ng/mL is considered GHD, while a response between 3 and 10 ng/mL is considered an intermediate response. A response of greater than 10 ng/mL is considered normal without evidence of GHD [21]. In the studies mentioned above, patients demonstrated a positive response to GH if their response to the GST was abnormal (i.e., less than 8 ng/mL). This is in keeping with a process whereby there is a spectrum of GH response to stimulation and not a simple all-or-nothing phenomenon. The mechanism underlying a chronic disease process resulting in abnormal GH secretion is unknown.

Patients typically present to healthcare providers with symptoms that can be classified into one of two categories: fatigue or cognitive dysfunction. The fatigue associated with TBI, as mentioned above, is profound and causes life changes for the patient. Because the patient cannot manage their symptoms related to fatigue, they may decide on making major life changes, such as retire from employment, work on a part-time basis, or seek a different vocation altogether that better fits their experience of fatigue. Fatigue symptoms typically do not fluctuate as they are persistent and all consuming. Reports of sleep disturbance are also common. Cognitive dysfunction, on the other hand, centers around three main complaints: (1) loss of short-term memory, (2) slowed processing speed, and (3) executive dysfunction. We named this syndrome Brain

Injury–Associated Fatigue and Altered Cognition (BIAFAC). When these patients are tested with GST and found to have abnormal GH secretion, replacement with GH can significantly improve their symptoms. Typically, symptoms related to fatigue are the first to improve within 2–3 months following initiation of GH replacement, whereas cognitive impairment can show signs of improvement 3–4 months post-GH treatment. Functional and cognitive symptoms can continue to improve up to 1 year following initiation of GH replacement; however, continued improvement is minimal. Cessation of GH replacement therapy will typically revert symptoms to baseline [68]. Studies are currently underway to understand the potential mechanisms causing BIAFAC and how GH is able to significantly improve the symptoms experienced by these patients.

For adults, very low levels of GH are used as replacement doses. For men and postmenopausal women, the maximum daily dose is 0.6 mg/day. For reproductive age women, 0.8 mg daily is the maximum dose. Initiation of GH replacement is usually tapered over time to prevent significant edema from the GH. A standard paradigm is to start with 0.2 mg daily for 2 months and then increase to 0.4 mg daily for 2 months and finally treat with 0.6 mg daily. Serum IGF-1 levels can be monitored with the dose increases to make certain that too much GH is not being given. The studies done with GH replacement used 400 ng/ml as an upper limit assessment of GH replacement without any significant side effects [9]. The side effects of low-dose GH replacement are few. For instance, patients may complain of generalized aches in their joints. Reducing the GH dose will usually relieve these symptoms. Carpal tunnel syndrome is a major concern, but carefully discussing the symptoms with the patient and lowering the GH dose if symptoms occur will minimize any need for surgical intervention. Insulin resistance is a concern, but its possibility is minimized with the low doses of GH used. If a patient develops cancer while on GH replacement, stopping the GH replacement is recommended, although there are no studies to our knowledge that address this concern. If this is a chronic disease process, there is the possibility that the disease can improve, and patients will not need GH replacement. GH "holidays" can be taken by patients to see if the symptoms return or whether they no longer need the GH to relieve symptoms.

Within the last decade, there have been select case reports and empirical studies that have assessed the influence of GH replacement in patients, particularly with moderate-to-severe TBI (Table 1). The findings from these more recent studies are promising and support the use of GH replacement as a treatment for cognitive, psychiatric, and physical/functioning impairment post injury. In their case series study of 6 patients with GHD and moderate-to-severe TBI, Maric and associates reported improvements in psychological, social, and cognitive functioning following 6 months of GH replacement [68]. Further, these cases were re-assessed 12 months after discontinuation of GH replacement. In the 4 (out of 6) patients that received GH replacement, declines were noted in self-reported symptoms related to depression, whereas more variable findings were noted on a brief, multidimensional, self-report personality inventory designed to screen a broad range of psychological problems. There was a noted worsening of symptoms following cessation of GH replacement in three dimensions of the personality inventory, including interpersonal sensitivity, anxiety, and paranoid ideation. Of the 2 patients who did not receive GH replacement, one did not demonstrate any significant changes, whereas the other demonstrated a significant increase in psychological symptoms on multiple psychiatric parameters. As for cognitive test performances, modest improvements for those patients receiving GH replacement were noted on tasks that assess verbal memory, nonverbal memory, confrontation naming, and executive functions, but not on a test of cognitive flexibility. In their case series study of 13 patients with moderate-to-severe TBI (including children, adolescents, and adults), Devesa and coauthors reported both cognitive and motor improvements with those patients with moderate TBI, demonstrating more prominent changes following GH

Table 1 Active growth hormone (rhGH) replacement studies (2010–2017)

Author(s), Journal	TBI patient sample	Title	Findings
High et al. 2010, J Neurotrauma, 27, 1565–1575 [19]	Moderate-to-severe TBI – Adult *N* = 23 (12 active rhGH; 11 placebo); All GHD or GH insufficient	Effects of growth hormone replacement therapy on cognition after TBI	Active rhGH group demonstrated significant performance improvements over time compared to placebo group on neuropsychological tests that assess memory, processing speed, executive functions, and motor dexterity and speed (dominant hand).
Maric et al. 2010, J Endocrinol. Invest., 33, 770–775 [68]	Moderate-to-severe TBI – Adult *N* = 6 (4 active rhGH; 2 control); All GHD; case series	Psychiatric and neuropsychological changes in growth hormone–deficient patients after TBI in response to growth hormone therapy	The majority of patients who received active rhGH demonstrated symptom improvement as determined by mood (depression) and personality inventories as compared to the control patients. Similarly, patients receiving active rhGH demonstrated modest improvements in neuropsychological tests that assess memory, visuoconstruction, visuomotor speed, and executive functions. Following discontinuation of GH replacement, declines in cognition with increases in mood symptoms and maladaptive personality traits were noted.
Reimunde et al. 2011, Brain Injury, 25 (1), 65–73 [135]	Injury severity unknown – Adult; *N* = 19 (GHD = 11 [active rhGH]; GH sufficient = 8 [placebo])	Effects of growth hormone (GH) replacement and cognitive rehabilitation in patients with cognitive disorders after TBI	Both groups received cognitive rehabilitation throughout the intervention. The active rhGH and control groups both demonstrated cognitive improvements over time. Within-group comparisons revealed that the active rhGH group demonstrated significant improvements in more cognitive parameters than the control group. Further, between-group comparison revealed that the active rhGH group performed significantly better on tasks that assess verbal abstraction, expressive vocabulary, verbal intelligence quotient, and full-scale IQ.
Devesa et al. 2013, Hormones and Behavior, 63, 331–344 [83]	Severe TBI – Child, adolescent, & adult; *N* = 13 (5 GHD; 8 GH sufficient); case series	Growth hormone (GH) and brain trauma	TBI patients (GHD & GH sufficient) received clinical rehabilitation and GH treatments. Each case demonstrated improvements in physical and cognitive abilities during active rhGH treatments than had been observed during clinical rehabilitation alone.
Moreau et al. 2013, J Neurotrauma, 30, 998–1006 [134]	Mild, moderate, and severe TBI – Adult; *N* = 50 (GHD = 23 [active rhGH]; GH sufficient/ insufficient = 27 [placebo])	Growth hormone replacement therapy in patients with TBI	Cognitive, ADL, & QoL assessments were performed at baseline and 12 months. A session effect was noted for all patients. An interaction effect revealed modest improvements for the active rhGH group on a task of visuospatial incidental learning and 2 out of 6 factors on a QoL inventory.

(continued)

Table 1 (continued)

Author(s), Journal	TBI patient sample	Title	Findings
Mossberg et al. 2017, J Neurotrauma,34, 845–52 [136]	Mild, moderate, and Severe TBI; *N* = 15 (all GHD [active rhGH]	Functional Changes after Recombinant Human Growth Hormone Replacement in Patients with Chronic TBI and Abnormal Growth Hormone Secretion	Peak cardiorespiratory capacity, body composition, and muscle force testing were assessed at baseline and 1 year after rhGH replacement. Additionally, standardized neuropsychological tests that assess memory, processing speed, and cognitive flexibility as well as self-report inventories related to depression and fatigue were also administered. Peak O_2 consumption, peak oxygen pulse (estimate of cardiac stroke volume), and peak ventilation all significantly improved. Maximal isometric and isokinetic force production was not altered. Skeletal muscle fatigue did not change, but the perceptual rating of fatigue decreased. Cognitive performance did not change significantly over time, whereas self-reported symptoms related to depression and fatigue demonstrated modest improvements.

GHD Growth hormone deficiency, *TBI* Traumatic brain injury, *ADL* Activities of daily living, *QoL* Quality of life

replacement and ongoing rehabilitation services [83]. High and colleagues reported on the cognitive effects of GH replacement in patients with moderate-to-severe TBI over a year [19]. In their double-blind, placebo-controlled study, 12 patients received active medication and 11 patients received placebo. Given the small sample size, both GHD and GH-insufficient patients (GST peak, 3–8 ng/mL, respectively) were grouped together. Cognitive and motor improvements for patients in the active medication group were discovered on tasks that assessed verbal learning, information-processing speed, executive functions, and motor dexterity and speed for the dominant hand compared to the control group. Similarly, Moreau and coauthors evaluated the effects of year-long GH replacement in patients with moderate-to-severe TBI compared to a brain-injured, age-matched control group [134]. Their findings revealed moderate improvements in memory (i.e., immediate memory) and information-processing speed. Improvements on tests of executive functions, attention, or language were not reported. More pronounced improvements were discovered in patients with greater levels of injury severity. In another study, Reimunde and coauthors assessed the impact of GH treatment in patients with moderate-to-severe TBI (11 active GH; 8 placebo) [135]. Following 3 months of GH replacement, they discovered improvements on tests of more crystallized skills including vocabulary, verbal intelligence quotient, and full scale IQ on the Wechsler Intelligence Scale (WAIS). Lastly, Mossberg and coauthors reported positive physical functioning and psychological changes, but not cognitive improvements, in 15 patients with mild-to-severe TBI replaced with GH for 1 year [136]. Peak $VO_{2\,max}$, peak oxygen pulse (an estimate of cardiac stroke volume), and peak ventilation were all significantly improved compared to baseline. Maximal isometric and isokinetic force production remained unchanged. Skeletal muscle fatigue did not change significantly; however, patients' self-reported rating of fatigue was reduced (statistical trend). Cognitive performance did not improve significantly, although self-reported symptoms related to depression did decrease significantly.

Conclusion

A moderate-to-severe TBI is both disease-causative and disease-accelerative [31]. There may be many other clinical manifestations of this chronic disease process that are currently uncharacterized or not fully understood. For instance, a recently published study assessed the absorption of amino acids following consumption of a nutritionally balanced meal in patients with moderate-to-severe TBI (residing in long-term care facilities) compared to age-matched, noninjured control subjects [137]. Results from their study collected in two separate facilities in different regions of the United States demonstrated that patients with TBI had abnormal levels of essential amino acids compared to control participants after a standard meal. The cause of the abnormal levels is not known, but the clinical significance of the abnormal levels could affect skeletal muscle, neurotransmitters, and metabolism. More specifically, early diagnosis and subsequent treatment can improve outcomes. However, PTH typically is not identified or treated due to masking effects of impairments secondary to damage to brain parenchyma other than the pituitary. Further, in the case of mTBI, while there is evidence of pituitary deficits, patients might not present to a physician for months following an injury or not at all. Because the chronic disease process post TBI is not clearly defined, many patients are suffering from BIAFAC, as discussed in this chapter, without the medical awareness that GH replacement is an option for management or resolution of cognitive, psychiatric, or physical/functioning sequelae. Continued research is needed to further define moderate-to-severe TBI as a chronic disease process and to increase our understanding of underlying mechanisms in order to develop treatments for improvements in functional outcomes and QoL in this patient population.

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