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A clinical and pathophysiological approach to traumatic brain injury-induced pituitary dysfunction

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Abstract

Purpose This review aimed to evaluate the data underlying the pathophysiology of TBI-induced hypothalamo-pituitary dysfunction.

Methods Recent literature about the pathophysiology of TBI-induced hypothalamo-pituitary dysfunction reviewed.

Results Traumatic brain injury (TBI) is a worldwide epidemic that frequently leads to death; TBI survivors tend to sustain cognitive, behavioral, psychological, social, and physical disabilities in the long term. The most common causes of TBI include road accidents, falls, assaults, sports, work and war injuries. From an endocrinological perspective, TBIs are important, because they can cause pituitary dysfunction. Although TBI-induced pituitary dysfunction was first reported a century ago, most of the studies that evaluate this disorder were published after 2000. TBI due to sports and blast injury-related pituitary dysfunction is generally underreported, due to limited recognition of the cases.

Conclusion The underlying pathophysiology responsible for post-TBI pituitary dysfunction is not clear. The main proposed mechanisms are vascular injury, direct traumatic injury to the pituitary gland, genetic susceptibility, autoimmunity, and transient medication effects.

Keywords Traumatic brain injury · Pituitary dysfunction · Pathophysiology · Antipituitary antibodies

Traumatic brain injury

Traumatic brain injury (TBI) is defined as a disruption in the normal function of the brain, owing to a bump, blow, or jolt to the head or a penetrating head injury [1]. TBI is a condition that demands serious attention; a sentence attributed to Hippocrates, "no head injury is too severe to despair of, nor too trivial to ignore" aligns with the criticality of TBIs.

The term "silent epidemic" is frequently used to characterize the worldwide incidence of TBI: it is generally underestimated, given its silent nature and the absence in many parts of the world of injury monitoring or reporting systems [2, 3]. TBIs contribute to death and disability more so than any other traumatic insult. In a recent systematic review, the pooled annual incidence rate was 349 per 100,000 person-years (95% CI 96–1266) across all age groups, with significant heterogeneity among studies [3]. The pooled annual incidence proportion of mild TBI was reported as 224 per 100,000 (95% CI 120–418); that of moderate TBI was 23 per 100,000 (95% CI 18–29), while that of severe TBI was 13 per 100,000 (95% CI 10–18) [3].

The most common cause of TBI is road accidents, followed by falls, assaults, work and war injuries. In low-income countries, those who sustain a TBI are generally young adult pedestrians, cyclists, or motorcyclists. In high-income countries, motor vehicle accidents constitute an important cause of TBI, although among individuals in older age groups, falls reportedly constitute the main cause of TBIs [4]. In regions where the prevalence of armed violence is higher, assault and blast injuries are important causes of TBIs [4]. Sports-related TBIs hold a special place in the TBI etiology: they are considered a subgroup of mild TBI, as sports activities tend to cause chronic and repetitive head trauma that affects a substantial number of athletes [5]. Contact sports like boxing, kickboxing, football, soccer, and ice hockey are examples of sports where TBIs commonly occur.

Relatively few cases of TBI are fatal, but most survivors live with cognitive, behavioral, psychological, social, and physical disabilities in the long term. From the

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endocrinological perspective this is important, because TBI can cause neuroendocrine disorders like hypopituitarism (HP). Although there has been growing awareness over the last 20 years of the prevalence of TBI-induced pituitary dysfunction, the signs and symptoms of pituitary dysfunction may be subtle and overlap with the neurological and psychiatric sequelae of head trauma; this can often lead to missed or delayed HP diagnosis.

In the current study we reviewed the data about pathophysiology of TBI-induced hypothalamo-pituitary dysfunction.

Hypopituitarism after traumatic brain injury

Although TBI-induced HP was first reported a century ago, most of the studies that evaluate this disorder were published after 2000 [6]. Recent studies reveal TBI as a leading cause of HP. The prevalence rate of post-TBI anterior HP is reportedly 27.5% [7]. Predictors of long-term pituitary dysfunction after TBI were evaluated in a recent extensive review [8]. These are; the severity of brain injury on admission computed tomography scan, increased intracerebral pressure (ICP), diffuse axonal injury (DAI), older age, acute pituitary hormone changes, length of stay in intensive care unit (ICU), presence of anti-pituitary antibodies (APAs) and anti-hypothalamus antibodies (AHAs) and basal skull fracture [7–13].

Pathophysiology of traumatic brain injury-induced hypopituitarism

The pathophysiology of TBI is complex. The primary mechanical event has impacts on the course of hypothalamic-pituitary function, as do secondary insults such as hypotension, hypoxia, ICP, and changes in cerebral blood flow and metabolism [14]. Although the etiology of post-TBI pituitary hormonal dysfunction is not completely understood, existing evidence suggests that multiple factors are relevant, including vascular injury, direct traumatic injury to the pituitary, genetic susceptibility, autoimmunity, and transient medication effects (Table 1).

Vascular injury is a widespread mechanism, as evidenced in autopsy studies that demonstrate pituitary infarction in up to 43% of all fatal TBI cases [15]. The anatomy of the pituitary gland and its blood supply makes the gland vulnerable to vascular injury. The pituitary gland is located within the bony sella turcica in the skull base. It is separated from the suprasellar cistern by the diaphragma sella and is tethered to the hypothalamus by the infundibulum. The adeno-hypophysis and neuro-hypophysis receive their blood supply primarily from the internal carotid arteries. The long hypophyseal portal vessels arise from the superior hypophyseal artery branches of the internal carotid artery and pass through the diaphragma sella; these vessels provide the anterior pituitary gland with 70–90% of its blood supply [16]. The anatomic extension of the long hypophyseal vessels makes them more susceptible to damage. Shearing forces—as well as compression by ICP, brain swelling, and brain shift—can cause ischemia of the pituitary gland. The short hypophyseal portal vessels arise from branches of the intracavernous internal carotid artery (i.e., the inferior hypophyseal arteries), which enter the sella from below the diaphragma sella and supply the anterior gland with less than 30% of its vascular supply, predominantly in the medial portion of the gland that includes the pars intermedia [16]. As a result, anterior lobe hormone deficiencies are frequently seen and the somatotroph and gonadotroph axes in the lateral wedge of the pituitary gland and supplied by long hypophysis vessels are most susceptible to post-TBI pituitary dysfunction [10, 12, 17]. The corticotrophs and thyrotrophs are located in the protected median wedge of the anterior pituitary and are anatomically less vulnerable to injury [17, 18].

Fractures through the skull base and sella turcica, as well as rotational and shearing injuries to the brain stem and hypothalamic-pituitary axis, may directly injure the pituitary gland or infundibulum [14]. Subsequent hemorrhage into the sella turcica or pituitary gland itself can further compromise pituitary integrity. Postmortem studies reveal a high prevalence of necrosis or hemorrhage into the pituitary gland,

Table 1 A summary of proposed mechanisms of pituitary dysfunction after TBI

1. Hypoxic insult
2. Axonal injury
3. Inflammatory changes
4. Autoimmunity
5. Genetic
6. Direct mechanical injury to the hypothalamus, pituitary gland or pituitary stalk
7. Compression from haemorrhage, edema or increased intracranial pressure
8. Vascular injury (brain edema, pituitary edema)
9. Systemic shock associated with vasospasm
10. Interruption of portal blood supply (due to high ICP)
11. Decreased cerebral spinal fluid flow due to ependymal ciliary loss which potentially negatively affects waste and nutrient exchange

which suggests a direct traumatic injury to the pituitary gland as another possible mechanism [19, 20].

A concussion is defined as a mild TBI that causes a sudden and transient impairment of neural functions; it is the most frequently occurring type of brain injury. It generally relates to sports-related brain injury, and it occurs after a direct blow to the head or after a trauma that occurs at any body site where impulsive forces are transmitted to the brain [21]. Concussion is thought to be a type DAI, because axons may be injured due to stretching [22, 23]. Histopathological examinations have shown sequential post-DAI changes, including disrupted axonal transport, secondary axonal disconnection, and Wallerian degeneration [23]. Repeated concussions can cause insidious neurodegenerative processes leading to chronic traumatic encephalopathy. Autopsy examinations of individuals with histories of exposure to repeated concussions have shown macroscopic and microscopic abnormalities, including brain atrophy, ventricular dilation, and tau/amyloid-β accumulation [24].

Apolipoprotein E (ApoE) is a plasma lipoprotein responsible for transporting cholesterol and lipids throughout tissues, including those of the central nervous system [25]. In the brain, ApoE is predominantly synthesized by astrocytes, microglia, and injured neurons [26]. ApoE affects the clinicopathological consequences of TBI by regulating amyloid deposition, lipid distribution, mitochondrial energy production, and oxidative stress [27, 28]. ApoE also increases intracellular calcium in response to injury [29]. TBI studies have shown that specific genetic polymorphisms in the ApoE gene coding region are associated with TBI prognosis [25].This gene codes the lipoprotein isoforms E2, E3, and E4. ApoE2, ApoE3, and ApoE4 differ in terms of amino acid sequence. A considerable body of evidence indicates that the ApoE genotype influences post-TBI outcomes [25], and ApoE4 shows postconcussion protective effects [30]. Genetic susceptibility can also establish a ground to HP after TBI. Tanriverdi et al. showed that the ApoE3/E3 genotype reduces the risk of post-TBI HP [31].

Autoimmune-mediated pituitary dysfunction has also been postulated. Head trauma may trigger an ongoing process like autoimmunity or neuroinflammation [32, 33]. Following head trauma, secondary neuronal injury is associated with a neuroinflammatory response, resulting in the release of reactive oxygen species and inflammatory cytokines, such as tumor necrosis factor, interleukin-1 (IL-1), and IL-6 [34]. ApoE has been found to reduce this neuroinflammatory response [35]. Head trauma may also cause disruption to the blood–brain barrier, causing brain proteins (especially sequestered pituitary and hypothalamic antigens from injured/necrotic tissue) to leak into circulation, thus evoking an immune response [36]. Tanriverdi et al. examined 29 patients who had undergone a 3-year post-TBI follow-up, as well as 60 age- and sex-matched controls; they evaluated pituitary function and anti-pituitary antibodies (APAs). APAs were detected in 44.8% of the TBI patients, but in none of the controls. The pituitary dysfunction development ratio was significantly higher among the APA-positive patients (46.2%) than the APA-negative ones (12.5%) [37]. In another controlled study [38], 61 boxers were evaluated for anti-hypothalamus antibodies (AHAs) and APAs. AHAs and APAs were detected in 21.3% and 22.9% of the boxers, respectively, but in none of the controls. Pituitary dysfunction was significantly higher among AHA-positive boxers than among AHA-negative ones.

In the acute intensive care unit (ICU) phase of injury, cortisol levels can be significantly suppressed by the administration of commonly used medications, including etomidate and metabolic suppressive agents (e.g., pentobarbital and propofol) [39]; however, the effects of medications are generally transient.

Most acute-phase hypopituitarism patients recover their pituitary function over time. The possible mechanism at work may stem from a direct mechanical injury that would not cause pituitary infarction, reversible edema formation, ICP, and hypoperfusion due to reversible vasospasm. An early histopathological study demonstrated that injured portal vessels can regenerate and grow down into the surviving areas of the anterior lobe [40].

Experimental models of traumatic brain injury-induced hypopituitarism

A few standardized animal studies provide insights into the mechanisms of posttraumatic HP. In a study by Greco et al., adolescent rats were exposed to a sham injury, single injury, or four repeated injuries. Circulating levels of basal growth hormone (GH) and insulin-like growth-factor-1 (IGF-1) were measured at baseline and at each of 24 h, 72 h, 1 week, and 1 month postinjury. The study results showed that repeated TBI significantly disrupted the GH/IGF-1 axis [41]. Additionally, the results of animal studies showed that IGF-1 has a neuroprotective role in maintaining normal brain function [42, 43]. GH and IGF-1 provide brain repair mechanisms and neuronal recovery following trauma, by regulating a number of factors (e.g., neuronal plasticity, myelin formation, and vascular tone) [44, 45].

Additionally, Osterstock et al. showed that by inducing a controlled cortical impact in mice, GH deficiency can be induced [46]. They showed that GH deficiency was due to hypothalamic changes. In that study, hypertrophied astrocytes were seen both within the arcuate nucleus and the median eminence, two pivotal structures of the GH axis; growth hormone-releasing hormone (GHRH) neurons, however, remained unaltered. In the median eminence, injured mice exhibited damaged distributions of claudin-1 and zonula occludens-1 between tanycytes, suggesting tight junction disruptions. They concluded that this alteration of the third ventricle might disrupt communication between the hypothalamus and the pituitary gland [46].

Kasturi et al. studied cortical contusion injury in young adult male rats and found that it led to GH deficiency 2 months postinjury. They found the upregulation of IL-1b and glial fibrillary acidic protein levels in the cerebral cortex, hypothalamus, and anterior pituitary. Based on these findings, the authors concluded that the chronic change they witnessed was likely the result of systemic and persistent inflammatory changes in the hypothalamus and pituitary [47].

Russell et al. found that the hypothalamic-pituitary-adrenal (HPA) axis responds to mild blast TBIs (mbTBIs) in a sex-dependent manner. They examined central and peripheral HPA axis reactivity 7–10 day after mbTBI, in both male and female mice. Male mice exposed to mbTBI had increased restraint-induced serum corticosterone (CORT) levels, but attenuated restraint-induced corticotropin-releasing factor (CRF)/c-Fos-immunoreactivity in the paraventricular nucleus (PVN) of the hypothalamus. Female mice displayed opposite responses, with attenuated restraint-induced CORT and enhanced restraint-induced PVN CRF/c-Fos-immunoreactivity. Russell et al. showed that the HPA axis of both male and female mice is susceptible to TBI; however, the profile of reactivity differed in a sex-dependent manner, and so they concluded that male and female mice use different strategies to cope with mbTBI-induced HP [48].

Sports-related traumatic brain injury and hypopituitarism

Sports-related injuries are generally underreported, due to the limited recognition of cases. The precise annual incidence rate of sports-related TBI in the United States is thought to range from 300,000 to 3.8 million cases per year [49]. A recent systematic review reported a total of 4788 adult sports-related TBIs in the National Trauma Data Bank of the United States between 2003 and 2012. Equestrian sports were the greatest contributors to sports-related TBI (45.2%); falls and interpersonal contact sports, roller sports, skiing/snowboarding, and water sports followed, in that order. Mild TBI represented nearly 86% of all injuries [50]. Concussion is defined as a mild TBI that causes a sudden and transient impairment of neural functions; it is the most frequently occurring type of sports-related brain injury. It occurs after a direct blow to the head, or after a trauma that occurs at any site of the body where impulsive forces are transmitted to the brain [21].

HP following a sports-related brain injury has been evaluated more recently, albeit in a limited number of sports. Kelestimur et al. was the first to show HP in a group of boxers. In that preliminary study, the pituitary functions of 11 actively competing or retired male boxers were compared to those of healthy controls. Prior to the study, none of the boxers showed any symptoms suggesting a pituitary hormone deficiency. GHRH + Growth Hormone Releasing Peptide-6 testing determined that the mean peak GH level in boxers was lower than that of the control group, while mean IGF-1 levels were significantly higher in the control group. There was a significant negative correlation between peak GH levels and boxing duration, and between peak GH levels and the number of bouts [21]. In 2008, Tanriverdi et al. evaluated pituitary functions in a larger group of boxers. Of the 61 amateur boxers included in the study—whose pituitary volumes were additionally investigated—15% had a GH deficiency and 8% had an adrenocorticotropic hormone (ACTH) deficiency. The boxers with a GH deficiency had a significantly lower pituitary volume than those with a normal GH [51]. In another study by Tanriverdi et al. [22] amateur kickboxers who had boxed in national and international championships were compared to healthy controls [52]. The IGF-1 levels of the kickboxers were significantly lower than those of the controls; additionally, 22% and 9% of the 22 kickboxers had a GH deficiency and an ACTH deficiency, respectively. There were significant negative correlations between IGF-1 levels and each of age, duration of sports participation, and the number of bouts [52]. These study results indicate that, as a result of partaking in combative sports, athletes can sustain repetitive mild head trauma, and that it can have a cumulative effect in terms of the development of pituitary dysfunction. (The total numbers of matches may reach 850 in boxers and 4800 in kickboxers [21, 52].) Zetterberg et al. showed that chronic trauma in boxers caused an increase in neuron-specific enolase, a glycolytic enzyme showing brain injury [53].

Kelly et al. evaluated pituitary and metabolic functions and quality of life (QOL) among 68 retired National Football League players [54]. Overall, hormonal deficiency was found in 23.5% of participants, with 14.7% showing an isolated growth hormone deficiency (GHD); 4.4% had isolated hypogonadism; and 4.4% had both GHD and hypogonadism. Metabolic syndrome and hypogonadism were seen in 50% and 83% of subjects, respectively. In this cohort of retired football players who were experiencing poor QOL, 23.5% had a hormone deficiency—including 19% with GHD and 9% with hypogonadism—and 50% had metabolic syndrome [54].

There are single case reports of post-TBI pituitary dysfunction in swimming and soccer sports [55, 56]. There has been an insufficient number of studies on sports-related TBI and HP incidence in terms of identifying the extent of the situation. Frequently, HP symptoms are often masked by trauma and postconcussion symptoms, and sports medicine clinicians should be alert to the possibility of pituitary disorders following sports concussion.

Blast-related traumatic brain injury and hypopituitarism

Between 2000 and 2016, the US Department of Defense (DOD) reported a worldwide total of 361,092 cases of TBI (DOD worldwide numbers for TBI, 2017). These included approximately 297,478 incidences of mild TBI (~82%), 32,951 of moderate TBI (~9%), and 3,770 of severe TBI (~1%); 21,828 of these head injuries (~6%) remained unclassified. The DOD data include all TBIs seen worldwide, including nonblast TBIs caused by vehicle crashes, falls, sports injuries, recreational activity, and military training. Penetrating and other severe head injuries comprised only 2.4% of this total.

Although there is extensive documentation pointing to the high prevalence of hypopituitarism following TBI from all causes, a limited number of studies evaluate pituitary gland dysfunction after blast-related TBI. In 2012, for the first time, preliminary data were captured supporting the high prevalence of chronic hypopituitarism among US military veterans deployed to Iraq or Afghanistan and who had sustained one or more blast-related concussions; the prevalence rate was compared to that of similarly deployed veterans without blast exposure [57]. In that study, 11 of 26 (42%) combat veterans who had served in Iraq or Afghanistan had abnormal circulating hormone concentrations in at least one axis, consistent with HP. Deficiencies in the GH–IGF-1 and pituitary-gonadal axes were observed most frequently [57]. Among those who had sustained blast injuries, a primary blast wave or wind may have caused direct injury to brain; additionally, secondary injuries can be inflicted by explosion debris or the impact of being thrown by a blast [58, 59]. These injuries could affect the hypothalamus, pituitary gland, or pituitary stalk, resulting in damage to cell bodies; they could also cause DAI or vascular injury.

In another study by Ioachimescu et al. 20 male veterans were diagnosed at the Veteran Administration Medical Center of Atlanta with mild TBI incurred during combat [60]. In 85% of cases, TBI was due to blast injuries; that number for falls and blunt head trauma was 10% and 5%, respectively. The amount of time since the most recent injury ranged from 8 to 72 months. This study showed a GHD prevalence rate of 25% among veterans with combat-related mild TBI, based on the results of glucagon stimulation tests; additionally, the GHD group exhibited more depression and lower QOL, relative to controls [60]. Undurti et al. recently evaluated the circulating hormone levels of 59 male US Armed Forced veterans with documented hazardous duty experience in Iraq and/or Afghanistan [61]. Thirty-nine of those individuals had sustained at least one explosive blast-induced concussion; the remaining 20 veterans (i.e., the deployment control group) had been exposed to similar deployment conditions but had not experienced a blast-related TBI. Twelve of the 39 mild TBI participants (31%) and three of the 20 veterans in the deployment control group (15%) screened positive for one or more neuroendocrine disorders. Positive screens for GH deficiency occurred most frequently. Analysis of the responses given via self-reported questionnaires revealed the main effects of both mild TBI and hypopituitarism on postconcussive and posttraumatic stress disorder symptoms [61].

Clinical presentation

Acute hypopituitarism

Acute-phase TBI occurs in the first 2 weeks following trauma, while the chronic phase starts 3 months later [62]. To date, there have been at least 10 studies to have evaluated hormonal changes in acute-phase TBI [11, 18, 63–70]. The prevalence rate of HP has been reported to be as high as 78% in acute-phase TBI [67]. Most of the acute-phase pituitary hormonal changes are adaptive (i.e., physiological responses to critical illness). It is difficult to estimate the true prevalence rate of HP in acute-phase TBI, and drawing hormonal changes from critically ill patients' hormone profile is difficult; undertaking dynamic tests during this phase is generally not feasible. Gonadotropin deficiency is the most common hormonal disorder, followed by GH deficiency. Decreased thyroxin (T4), cortisol, and anti-diuretic hormone levels are other hormonal deficiencies encountered in acute-phase TBI. Hyperprolactinemia may also be seen, on account of stress response or stalk injury. In a study whose subjects had sustained an increased level of prolactin, low free triiodothyronine (fT3), fT4, and cortisol levels closely correlated with TBI severity [63]. In any case, the focus during the acute phase of brain injury should be on detecting adrenal insufficiency, as an undetected cortisol deficiency can be life-threatening. Up to 78% 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 [39]. Hannon et al. showed that acute hypocortisolemia was predictive of mortality and long-term pituitary deficits [67]. An acute-phase cortisol level below 11 μg/dl (300 nmol/l) is suggestive of adrenal insufficiency. In the acute ICU phase of injury, cortisol levels can also be significantly suppressed by commonly used medications, including etomidate and metabolic suppressive agents (e.g., pentobarbital and propofol) [39].

Chronic hypopituitarism

Two large meta-analysis and systemic reviews evaluated the epidemiology of chronic-phase TBI-induced hypopituitarism; one was in 2007, and the other in 2014 [7, 13]. The first meta-analysis featured 13 studies of 809 TBI patients; in that study, the pooled prevalence rate of post-TBI anterior hypopituitarism was 27.5% (95% CI 22.8–28.9%). In the second meta-analysis, 66 studies featuring 5,386 TBI patients evaluated the HP prevalence rate; in that study, 31.6% (95% CI 23.6–40.1%) of the patients had at least one anterior pituitary disorder. Studies published after 2010 report incidence rates ranging from 5 to 68% [4, 9, 18, 54, 60, 61, 71–76]. This range is large, on account of differences among the studies in terms of the populations sampled, injury severity, time since injury, hormone measurement methods, and screening and clinical diagnostic criteria. Generally speaking, hormonal screening cannot, on its own and in the absence of provocative testing, provide conclusive evidence of clinically significant deficiencies; in fact, the use of hormonal screening alone may lead to HP overdiagnosis, and this may to a great extent explain the differences in these studies' results.

It is noteworthy that, in all courses of TBI, pituitary hormones show dynamic changes. Most patients with acute-phase hypopituitarism recover their pituitary function over time. A recent prospective study found that of the patients presenting with at least one hormonal deficiency, about 55% recovered their pituitary function within 3 months, and 74–85% within 1 year [18].

Conclusion

This study reviewed current data relating to traumatic brain injury (TBI)-induced hypopituitarism (HP) pathophysiology. Relatively recently, TBI has become newly understood as a cause of pituitary dysfunction. The prevalence rate of TBI-induced HP among patients is reportedly about 30%. Its clinical symptoms are generally subtle, and they may be overlooked if a clinician is unaware of the course of the TBI. Although the mechanism of post-TBI pituitary dysfunction is not completely understood, some mechanisms have been proposed (e.g., vascular injury, direct traumatic injury to the pituitary, genetic susceptibility, autoimmunity, and transient medication effects).

Compliance with ethical standards

Conflict of interest Sule Temizkan and Fahrettin Kelestimur declares that they have no conflict of interest.

Research involving human participants or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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