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Pituitary pathology in traumatic brain injury: a review

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Abstract

Purpose Traumatic brain injury most commonly affects young adults under the age of 35 and frequently results in reduced quality of life, disability, and death. In long-term survivors, hypopituitarism is a common complication.

Results Pituitary dysfunction occurs in approximately 20–40% of patients diagnosed with moderate and severe traumatic brain injury giving rise to growth hormone deficiency, hypogonadism, hypothyroidism, hypocortisolism, and central diabetes insipidus. Varying degrees of hypopituitarism have been identified in patients during both the acute and chronic phase. Anterior pituitary hormone deficiency has been shown to cause morbidity and increase mortality in TBI patients, already encumbered by other complications. Hypopituitarism after childhood traumatic brain injury may cause treatable morbidity in those survivors. Prospective studies indicate that the incidence rate of hypopituitarism may be ten-fold higher than assumed; factors altering reports include case definition, geographic location, variable hospital coding, and lost notes. While the precise pathophysiology of post traumatic hypopituitarism has not yet been elucidated, it has been hypothesized that, apart from the primary mechanical event, secondary insults such as hypotension, hypoxia, increased intracranial pressure, as well as changes in cerebral flow and metabolism may contribute to hypothalamic-pituitary damage. A number of mechanisms have been proposed to clarify the causes of primary mechanical events giving rise to ischemic adenohypophysial infarction and the ensuing development of hypopituitarism.

Conclusion Future research should focus more on experimental and clinical studies to elucidate the exact mechanisms behind post-traumatic pituitary damage. The use of preventive medical measures to limit possible damage in the pituitary gland and hypothalamic pituitary axis in order to maintain or re-establish near normal physiologic functions are crucial to minimize the effects of TBI.

Keywords Hypothalamic-pituitary autoimmunity (HP-A) · Pathology · Pituitary · Post traumatic hypopituitarism (PTHP) · Traumatic brain injury (TBI)

Introduction

In industrialized countries, traumatic brain injury (TBI) most commonly affects young adults under the age of 35 and frequently results in reduced quality of life, disability, and death [1]. During both the acute and chronic phase of TBI, long-term survivors may exhibit varying degrees of post-traumatic hypopituitarism (PTHP) [2–15]. The most frequently reported hormonal deficits include decreased growth hormone (GH) secretion and hypogonadism, followed by hypothyroidism, hypocortisolism, and diabetes insipidus [5–7, 16–27]. Anterior pituitary hormone deficiency may increase mortality in TBI patients already experiencing other complications [9]. In children, PTHP resulting from TBI may cause treatable morbidity yet, few children with head injuries are seen in endocrine clinics and many cases are

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not properly identified. The most commonly affected pituitary hormone is GH, but seldom is head injury identified as the cause of GH deficiency in those patients. Retrospective studies of hospital admissions show that TBI is common, but underreported. Prospective studies find that its incidence may be 10-fold higher than assumed since most cases are considered mild and the patients are not investigated in hospital [28].

Traumatic brain injury is a significant cause of morbidity and mortality both in the adult and pediatric population and is associated with significant financial and social burden [29]. In 2013, approximately 2.8 million emergency department visits, hospitalizations, and deaths were TBI-related in the United States [30]. TBI was identified in over 282,000 hospitalizations [30]. Moderate and severe traumas frequently result in devastating consequences and are often associated with significantly diminished quality of life and unemployment in adults, and compromised development in children [29]. The leading cause of TBI is attributed to falls (typically occurring in children and older people), followed by being struck by -or against- an object, motor vehicle accidents, and violent assaults/child abuse. Sports and recreational activities are associated with repetitive head trauma, with a cumulative effect on the development of pituitary dysfunction [31, 32].

The first documented case illustrating the relationship between head trauma and subsequent pituitary dysfunction was in 1918 [33], but it was not until the turn of this century that the incidence of pituitary dysfunction resulting from head trauma received much interest. Since then, a significant number of studies have shown the consequences of TBI resulting from even minor trauma [34] such as sport-related concussions [35–37], and blast-related mild TBIs in veterans [37–40] which led to PTHP [5, 6, 16, 17, 20–22, 41, 42]. In a study by Schneider et al., they systematically evaluated the frequency of PTHP occurring after TBI [20]. In a three months follow-up after experiencing head trauma, authors found that in 22 patients with mild, moderate, or severe TBI, 36.4% had presented with subnormal responses in at least one hormonal axis [20].

Pituitary gland

The pituitary gland is located within a protective bony structure -sella turcica- and attached to the brain by blood vessels and nerve cell projections. It is made up of several cell types that produce various hormones that control the endocrine activities of the thyroid, adrenal cortex, and gonads. The pituitary gland is divided into the adenohypophysis (anterior pituitary), which makes up 80% of the gland, and the neurohypophysis (posterior pituitary) forming the remainder. The adenohypophysis is composed of the pars distalis (anterior lobe or pars glandularis), pars intermedia, and the pars tuberalis (pars infundibularis) [43]. The vasculature of the gland is highly intricate. The superior and inferior hypophysial arteries, which originate from carotid arteries, form a superficial external and an internal plexus. The internal plexus consists of capillary loops that contribute to the formation of the hypophysial portal system. This system of blood vessels connects the hypothalamus to the anterior pituitary, and its chief function is the transport and exchange of hypothalamic releasing and inhibiting hormones that control the secretion of the pituitary hormone-producing cells. The anterior lobe has an exceptional pattern of circulation because it does not have direct arterial blood-supply and all the blood it obtains comes from the hypophysial portal vessels. [44]. 70–90% of the blood supply that nourishes the adenohypophysis is provided by the long portal vessels, while the shorter portal vessels which originate in the lower part of the pituitary stalk and the posterior lobe, provide the remaining 10–30% [43].

Clinical and epidemiological implications

The Glasgow coma scale (GCS), which is the most common scoring system used to assess the conscious state of a patient following a TBI, does not gauge whether the TBI has any effect on pituitary function. It is a useful and inter-rater reliable method of assessing the initial and subsequent changes in a patient after a brain injury; it is reliable and correlates well with the outcome following a TBI. GCS is designed for acute care management and does not provide any insight into the extent or location of the TBI. The GCS results may be distorted by various factors including the increased use of pre-hospital intubation, paralyzing and/or sedating agents, delayed assessment time between injury and grading, weak inter-observer reliability, and limitations in predicting outcome in pre-verbal subjects. Conversely, imaging studies facilitate the structural classification of TBI and play a crucial role in the diagnosis and interpretation of any possible pituitary changes and/or damage during the post-TBI period. Currently, magnetic resonance imaging (MRI) is the gold standard for pituitary imaging, but computed tomography (CT) scans of the brain are usually obtained acutely and may have predictive value as well. Various studies have shown the association between imaging results and PTHP. Schneider et al. found an association between basal skull fractures or diffuse axonal injury and PTHP, while in a separate study, Kelly et al. analyzed initial CT scans of the head and found that specific imaging findings, such as diffuse brain swelling could predict PTHP [20, 45].

Among pediatric (birth to 18 years of age) patients, there is a high incidence rate of TBI documented in young adults and those who have sustained head trauma in early

childhood as a result of an assault or other violent activity. An estimated 15–25 children per 100,000 annually are affected by abusive head trauma that results in severe TBI. Generally, the leading causes of TBI in late adolescence include injuries sustained as a result of motor vehicle accidents, as well as sports-related injuries from martial arts, ice hockey, or boxing. As expected, children are more prone to injuries due to slips and falls, being struck by objects- or struck against- objects, or from pedestrian traffic road accidents. Male individuals of all ages, as well as those with low socioeconomic status, and minority populations are all at higher risk of sustaining a TBI [28, 46].

The reported prevalence of pituitary dysfunction after TBI has differed significantly in publications due to variability in testing protocols, the timing of assessment, inclusion/exclusion criteria used to create sample groups, and data/reporting discrepancies of pituitary hormone deficiencies.

Zheng et al. investigated the changes in pituitary hormones in 164 TBI patients on various days (days 1, 7, 14, 21, and 28) following their injury. They assessed the severity of TBI upon admission and their long-term outcome using both the GCS score and the Glasgow Outcome Scale (GOS) score. Changes of their pituitary hormone levels were correlated with TBI severity and outcome. More than half of the patients investigated showed post traumatic pituitary dysfunction at 1 month that gradually resolved over time. GH, thyrotrophic hormone, and gonadotropic hormone were the most affected and showed the most significant deficiencies especially in cases of severe TBI. They concluded that close monitoring of pituitary hormone profiles in TBI patients might indicate the severity of the injury sustained and may also determine the outcome. Moreover, there was a strong association between the presence of these deficiencies and long-term neurological status [47].

Studies evaluating hormonal changes in TBI have shown that hormonal deficiencies may occur without a specific endocrine disease. In adult patients, rates of subclinical pituitary deficiency vary considerably (5–61%), while the overall rate in children is approximately 20% [28]. Most TBIs produce GH deficiency. Gonadotropin status is difficult to assess, but precocious puberty occurs in up to 12% of TBI cases studied. Post-traumatic hypopituitarism may persist 6–12 months post-injury and it has been shown that it will eventually resolve within 1–3 years post-TBI [28].

Pathogenesis

Although the exact mechanisms underlying PTHP have not yet been elucidated, various hypotheses have been proposed. A widely- accepted theory suggests that as a result of a TBI, there is an ischemic insult to the pituitary gland [26]. In a study by Dubourg and Messerer, they concluded that in addition to the primary traumatic incident, secondary intracranial insults including changes in cerebral flow and metabolism, as well as cerebral hypoxia, hypotension, and increased intracranial pressure might play a role in hypothalamic-pituitary damage [31]. Specific mechanisms have been proposed as the primary events that cause ischemic adenohypophysial infarction and the subsequent PTHP. The pituitary stalk which is connected to the anterior pituitary and hypothalamus, is structurally fragile and is vulnerable to the effects of TBI. Normal pituitary stalk function may be interrupted following brain trauma due to either pituitary stalk traumatic transection, or the compressive effect of increased intracranial pressure which may lead to ischemic damage and necrosis to the anterior lobe by restricting its supply of blood via the portal vessels [48–52]. Daniel et al. [49–51] investigated the pituitary stalk section effect in both laboratory animal models and in vivo in human patients who were diagnosed with generalized carcinomatosis. They observed a substantial amount of necrosis in the adenohypophysis and concluded that as a result of pituitary stalk damage, the long portal vessels that supply the anterior lobe were disrupted which led to the development of ischemic necrosis [48, 53, 54].

In the 1960s, hypophysectomy was performed on patients with advanced cancers [55]. Subsequently, the pituitary stalk section was used as an alternative to hypophysectomy in order to depress pituitary function. In a study of patients who underwent pituitary stalk section, researchers noted that patients who died in a short period following the procedure, they developed a large infarct that occupied the greater part of the lobe; patients who survived for a longer period of time post-surgery, had a collagenous scar in the central and anterior parts of the anterior lobe, with a clear demarcation between the scar and the surviving parenchyma [56]. In another large clinical study involving patients with space-occupying intracranial lesions, 12 out of 270 cases investigated had patchy adenohypophysial necrosis [54] resulting from mechanical factors, mass effects, and increased pressure due to TBI. The presence of the intracranial lesions caused lateral stalk displacement and extrinsic occlusion of portal vessel branches. In an earlier study, investigators suggested that the focal pattern of ischemic infarction could be linked to this specific etiology as compared to stalk amputation [50]. Although the hypotheses stating that pituitary stalk section and/or increased intracranial pressure affecting the stalk may offer a suitable elucidation for the ischemic necrosis observed following TBI, other causes should also be considered as contributing factors.

An alternative hypothesis which may also play a role in adenohypophysial ischemia and necrosis explored the possible effect of systemic ‘shock’ (circulatory collapse) on the adenohypophysis and pituitary gland [52]. Of particular interest in this connection is the study by Sheehan et al.

where they proposed this occurrence in cases that contained anterior pituitary necrosis linked to postpartum shock in which portal vasospasm was suspected to be a contributing factor [53]. Sheehan et al. also noted that adenohypophysial necrosis secondary to thrombosis of the portal vessels (without previous hypotension) may cause irreversible ischemic necrosis [53]. Studies by Daniel et al. also predicted that blood pressure irregularities, namely intra-operative hypotension and diabetes, may be linked to anterior pituitary necrosis due to shock in patients with non-obstetric conditions [50].

Vascular hypothesis

While the pathophysiology behind head trauma and PTHP is complex, the vascular hypothesis proposed by various researchers may provide a likely explanation to the mechanism(s) by which PTHP develops after TBI. The pituitary gland's anatomic extension of the long hypophysial vessels makes it more vulnerable to vascular injury. Since the anterior lobe of the pituitary gland receives its blood supply from the portal system [57], it is possible that damage to the long portal vessels, which have an anterolateral distribution in the gland, may result in hormone deficiencies frequently involving the lateral somatotroph and gonadotroph axes [58–60]. Evidence that supports the vascular hypothesis and PTHP is the pattern of hormonal loss and cellular distribution. It has been widely noted that both somatotrophs and gonadotrophs are largely susceptible to dysfunction post-TBI. These cells are located in the lateral wings of the anterior pituitary (somatotrophs) and pars tuberalis (gonadotrophs) to which the long hypophysial portal vessels are the main source of blood supply to those areas of the pituitary. Therefore, any injury, damage or infarction to the lateral or peripheral regions of the pituitary will most likely affect those two cell types [16, 19, 61].

Insults to the pituitary gland and vascular network along with the brain trauma, swelling/enlargement and hypoxia commonly associated with TBI may cause hemorrhage and necrosis to the pituitary which may result in PTHP. Imaging studies looking at both acute and chronic phases following TBI have demonstrated these pathological changes which are consistent with vascular injury. Schneider et al. noted that these abnormalities occurred in 80% of patients with PTHP compared to only 29% of patients without PTHP [62, 63].

In a study utilizing both CT and MRI, Benvenga et al. observed pituitary and/or hypothalamic lesions in 93% of the PTHP cases they studied [2]. Subsequent imaging studies confirmed the existence of chronobiologic pathologic vascular alterations in the pituitary present in the acute and chronic phases following brain injury [7, 59]. Maiya et al. emphasized the irregularities such as edema, hemorrhage, or infarction in 30% of TBI patients they investigated using MRI [63].

Neuroendocrine hypothesis

Traumatic brain injury may cause alterations in brain function and pathology due to the impact of external forces to the head. Taylor et al. documented attenuation of the stress response of the hypothalamic–pituitary–adrenal (HPA) axis and differential short- and long-term dysregulation of the neuroendocrine stress response post-TBI [64–66]. Due to its unique location, enlargement of the pituitary will compress the gland, since it rests in a protective bony enclosure covered by the sellar diaphragm [63]. In the case of traumatic forces, the pituitary or the infundibulum that is connected to the hypothalamus can be directly injured [67]. Pituitary stalk damage may disturb the chromophile cells that produce the pituitary hormones in the pars tuberalis, which will cause a reduction in the production of gonadotropins, ACTH, and TSH [68, 69]. Following a TBI, changes in the HPA axis include an increase in serum cortisol, interruption or halting of diurnal rhythm, and insufficient suppression following dexamethasone treatment. Although the levels of cortisol are initially increased, this is an adaptive mechanism in response to the acute injury response—mediated by ACTH—which gradually normalize over time [70, 71].

Data regarding the effect of TBI on prolactin levels are conflicting. Studies have reported elevated, normal or low levels of prolactin post-TBI [72–75]. Hyperprolactinemia after injury may be mediated by physical stress or secondary to pituitary stalk compression, which may affect dopaminergic inhibitory control [76].

Direct damage to the hypothalamus is not typically seen, but an injury to the structure of the infundibulum may also create additional pituitary deficiencies due to loss of hypothalamic input. Intracranial hypertension may increase apoptosis in the hypothalamus, pituitary, and hippocampus [77]. The exact prevalence of PTHP is not clear, and recent recommendations propose pituitary screening at 3–6 months post-injury especially in patients with prolonged hospital stays, or in patients showing symptoms of pituitary dysfunction [58, 72, 77].

Autoimmunity hypothesis (hypothalamic-pituitary autoimmunity)

In addition to the vascular and neuroendocrine theories, the concept of hypothalamic-pituitary autoimmunity has also been postulated due to accumulating data based on new research focusing on inflammatory infiltration of the pituitary. A recent article summarized consecutive case

reports in the emergence of this particular hypothesis [78]. It was initially described in a case report dating back to 1968 whereby a young woman developed hypopituitarism and later died of circulatory shock following surgery due to adrenal failure. This case was unique in that it was the first to show the coexistence of lymphocytic infiltration of the anterior pituitary along with an enlarged thyroid and adrenal gland. Authors suggested that these findings illustrated a systemic endocrine autoimmune disorder [79]. Although several candidate pituitary autoantigens, including candidate autoantigens in the 27 kDa pituitary cytosolic region, GH, pituitary gland specific factors 1a and 2 (PGSF1a and 2), secretograninII (SgII), α-enolase, and chorionic somatomammotropin have been recently described to be useful markers for the diagnosis of autoimmune disease, none have proven to be reliable as a diagnostic tool for pituitary disease [80, 81].

Apolipoprotein E (APOE) is a 34.2 kDa glycoprotein widely distributed in tissues and characterized by its many functions. Several studies have revealed that APOE has an inhibitory effect on the neuroinflammatory cascade following injury and that the APOE e3 isoform is more effective than the APOE e4 isoform [82]. In a study of 93 TBI patients, those with APO E3/E3 genotypes had been linked to a reduced risk to suffer from PTHP following TBI [37]. Thus, it may be speculated that secondary insults resulting from neuroinflammation and cytokines may be influential in the overall pathology of the pituitary following TBI [83]. It was also demonstrated that the expression of inflammatory mediators, such as interleukin (IL)-1β and reactive glial fibrillary acidic protein (GFAP) in the hypothalamus, anterior pituitary and cerebral cortex of rats increased after sustaining cortical contusion injury (CCI) [84]. Circulating anti-hypothalamic antibodies (AHAs) and antipituitary antibodies (APAs) play a role in the pathogenesis of PTHP [81]. Tanriverdi et al., first proposed the importance of autoimmunity in PTHP after they had identified the presence of APAs in 44.8% of TBI patients three years after they had sustained a TBI [37]. They found a correlation between individuals who were found to be APA-positive and increased risk of PTHP, and that elevated APA titers correlated with lower GH response to stimulation by GH releasing peptides (GHRH + GHRP-6). Hypothalamic or pituitary antibodies were present in 21.3 and 22.9% of the cases studied, respectively, whereas no APAs were identified in the controls [85]. They concluded that although AHA positivity was significantly associated with PTHP, APA positivity could not be conclusively associated with the same thing. Overall, it is important to note that these results increase the credibility of the significance of neuroinflammation in the pathogenesis of PTHP.

Pathologic changes

Given the location of the pituitary gland within the skull and the fact that the infundibulum connects it to the hypothalamus, it is no wonder that both the anterior and posterior lobes of the pituitary gland are susceptible to mechanical trauma as a result of a TBI. Mechanical injuries to the brain stem, the HPA axis, or fractures to the sella turcica, may damage or injure the pituitary or hypothalamus directly and subsequent hemorrhage into the sella turcica may cause further damage to the pituitary [86].

Various publications detailing autopsy case findings support the correlation between pituitary vascular vulnerability in TBI and PTHP. Early studies of over 200 TBI subjects [52, 87] revealed the presence of anterior pituitary necrosis in approximately 22% of the cases. A cornerstone study by Bevenga et al. reviewed many TBI cases and noted that in almost one-third of TBI fatalities they studied, pituitary dysfunction and necrosis was documented [2]. In a separate investigation focusing on the pathologic changes occurring after the patient immediately following a TBI compared to patients who survived from 3 h to 7 days after a TBI were studied [48]. Gross and microscopic evaluation revealed no pathological changes or necrosis in the cases where the patient died immediately following the trauma; however, 43% of the cases from the group that survived, showed varying degrees of hemorrhage and necrosis [48]. Detailed histologic examination of the pituitary tissues from this group demonstrated different phases of necrosis including focal (< 10%) in those who died within 1 day following a TBI, and extensive necrosis involving > 50% of the anterior pituitaries in patients who survived between 1 and 7 days post-TBI [48]. From the same study, tinctorial features using hematoxylin and eosin stained sections were analyzed and they found that chromophiles lost their staining properties, cell membrane, and nuclear pyknosis, indicating that those cells were most likely undergoing necrosis. The study also revealed that the capillaries of the complex vasculature around infarct areas in the anterior pituitary were congested and accompanied by microscopic hemorrhagic foci [48].

Systematic imaging studies correlating PTHP with pathological abnormalities of the pituitary by assessing the relationship between PTHP and MRI findings have shown that there is a higher incidence of chronic pituitary abnormalities documented in TBI patients with PTHP [7]. Researchers noted that the pattern of decreased pituitary volume along with signal heterogeneity could represent hemorrhage, fibrosis or necrosis and that the decrease in pituitary volume detected in the sella may be due to both increased intracranial pressure and pituitary necrosis [88].

In another MRI study that utilized diffusion-weighted imaging showed that patients diagnosed with TBI who

presented with decreased pituitary tissue, water diffusivity could be used as a marker for microstructural damage [89]. TBI patients who presented with PTHP exhibited lower water diffusivity values compared to those without PTHP. An experimental study by Molaie and Maguire investigating closed head injuries also showed the presence of pituitary damage along with neuroendocrine dysfunction secondary to TBI [58]. While experimental studies using rats noted that after recurrent TBIs, they experienced disruptions to the GH/IGF-1 axis and pituitary vascular damage [90, 91]. Neuronal apoptosis following head trauma has been linked to decreased levels of IGF-1 in rats who sustained tissue damage in the HPA axis and hippocampi [92]. In a study investigating the relationship between GHD and reduced pituitary volume estimations on MRI scans compared GH-deficient retired boxers and GH-normal boxers revealed lower pituitary volumes accompanied by lower GH levels in the GH- deficient group. The researchers hypothesized that the underlying mechanism responsible for the volume reduction and hormone deficiency may involve the triggering of plastic growth responses, namely hypoplasia or hyperplasia [93]. (Table 1)

Non-pituitary neuropathology of traumatic brain injury

It is common for pathologists and clinicians to classify TBI as focal and diffuse [94]. Among focal injury, stereotypical types include contusions, single or multiple epidural, subdural and subarachnoid hemorrhages, brain stem hemorrhage and/or infarction due to intracranial space-occupying lesions, i.e., abscess or pontocerebellar tears, pituitary stalk or cranial nerve avulsions. Moreover, the most commonly reported focal injuries include contusions, lacerations of the brain, pure intracerebral hematomas, and burst lobe lesions. In contrast, diffuse brain injury can present in different forms, i.e., diffuse axonal injury (DAI), hypoxic brain injury, brain swelling and diffuse vascular injury [94]. Posttraumatic neuropathological changes are designated as primary and secondary [95]. Primary post-traumatic neurologic associated changes consist of immediate alterations occurring immediately after the incident, but the secondary changes insidiously progress over a more extended period [95] and may include complex vascular and neuroinflammatory molecular interactions [96]. Susceptible regions for shear/strain and deformation effects may show local or regional brain atrophy [97–100]. Volumetric analysis by MRI revealed distinctive volume loss in the cingulate gyrus, anterior cingulum, and multiple regions within the frontal lobes as well as the cuneus and precuneus regions as well [101]. Theoretically, it was proposed that stretch and shearing effects resulting from a TBI are the underlying pathogenetic mechanism of Wallerian degeneration of long coursing frontoparietal connections [102]. Considering the effects on microstructural networks of the brain, in addition to morphological changes, a broad spectrum of molecular changes is also seen [91]. The function of the axolemma is to regulate the membrane ionic movement as the cytoskeleton, eventually forming the scaffolding for normal axon morphology [103]. Depending on the severity of the injury, if it is enough to induce physiological changes, it may not be sufficient to cause morphological changes. Nevertheless, neural transmission and function pursue without interruption. However, if the injury is time-limited, neuronal cellular disruption can be temporary.

In chronic traumatic encephalopathy (CTE), a broad spectrum of gross pathologic findings may be found [96]. These include reduced brain weight, cerebral atrophy, lateral and third ventricle enlargement, cavum septum pellucidum, septal fenestrations, locus ceruleus and substantia nigra depigmentation, as well as thalamic and hypothalamic atrophy, including the mammillary bodies [104]. Neuropathological features ranging from gross morphology to molecular alterations depending on severity, extent, and duration of the process may result in disruptions to the blood–brain barriers [105], abnormal perivascular and parenchymal fibrinogen, and immunoglobulin G (IgG) deposits in the cerebral cortex [106]. In chronic traumatic encephalopathy, CD68 positive reactive microgliosis [107], increased levels of cytokine CCL11 in the frontal cortex [108], presence of perivascular tau oligomers and exposure of an N-terminal motif in tau [109], axonal injury, myelin degeneration, and loss of white-matter are present. These may play a critical role in initiating p-tau pathology [110], co-localizing neuronal and glial TDP-43 protein inclusions [111, 112], accompanied by diffuse Aß-containing plaques [113].

Conclusions

There are a significant number of challenges in relation to the analysis, diagnosis, and management of TBI and PTHP. TBI causes a substantial amount of morbidity and mortality in both adults and children, and PTHP is too often underdiagnosed. Pituitary hormonal dysfunction may have an impact on the overall recovery process and quality of life issues in those patients. Although TBI is widespread in various sports and leisure activities, it is critical to not only diagnose any potential head injury but to also create a pragmatic approach to screen for possible damage or adverse effects of TBI on the body, including the pituitary gland. Endocrine testing may not be feasible to perform in every TBI associated case, but it should not be overlooked. Current data indicate that pituitary dysfunction resulting from TBI does pose a real issue to not only those who are affected

Table 1 Pituitary in TBI patients in representative reports in literature

Authors/years	Type of study/patients	Main observations
Cyran, 1918 [33]	Case report/1 case	Post-head trauma hypopituitarism (PTHP)
Sheehan, 1937 [53]	Postmortem/2 cases	First description: Post-partum necrosis of the anterior pituitary
Wolman 1956 [54]	Postmortem/270 cases	Pituitary necrosis in raised intracranial pressure
Daniel, 1958 [49]	Postmortem/Case report	Pituitary stalk section
Daniel, 1959 [50]	Postmortem/5 cases	Five cases in which extensive infarction of the anterior lobe, due to rupture of the pituitary stalk, was found at necropsy shortly after head injury
Daniel, 1961 [51]	Book chapter	The pathology of the pituitary gland in head injury. In: Gardiner-Hill H, editor. Modern trends in endocrinology. 2nd series. New York: Hoeber; 1961. pp 55–68
Ceballos, 1966 [52]	Series/102 cases	N.I.
Adams et al., 1966 [56]	Clinical study/21 cases	Transection of the pituitary stalk in man: anatomical changes in the pituitary glands of 21 patients
Kornblum 1969 [87]	N.I	Pituitary lesions in craniocerebral injuries
Lieberman 2001 [22]	Clinical study/7 cases	Prevalence of neuroendocrine dysfunction in patients recovering from traumatic brain injury
Agha 2004 [16]	Clinical study/85 cases	Anterior pituitary dysfunction in survivors of traumatic brain injury
Bondanelli 2004 [5]	Clinical study/50 cases	Occurrence of pituitary dysfunction following traumatic brain injury
Bondanelli 2005 [3]	Review	Hypopituitarism after traumatic brain injury. Eur J Endocrinol. 2005 May;152(5):679-91. Review
Aimaretti 2005 [4]	Clinical study/70 cases	Residual pituitary function after brain injury-induced hypopituitarism: a prospective 12-month study
Kelestimur 2004 [35]	Clinical study/11 cases	Boxing as a sport activity associated with isolated GH deficiency
Popovic 2005 [6]	Review	Hypopituitarism following traumatic brain injury (TBI): Call for attention
Leal-Cerro 2005 [21]	Clinical questionnaire/200 cases	Prevalence of hypopituitarism and growth hormone deficiency in adults long-term after severe traumatic brain injury
Tanriverdi 2007 [36]	Clinical study/22 cases	Kickboxing sport as a new cause of traumatic brain injury- mediated hypopituitarism
Salehi 2007 [48]	Postmortem study/42 cases	Histologic study of the human pituitary gland in acute traumatic brain injury
Tanriverdi 2008 [37]	Clinical study/61 cases	Brief communication: pituitary volume and function in competing and retired male boxers
Schneider, 2008 [20]	Clinical study/78 cases	Predictors of anterior pituitary insufficiency after traumatic brain injury
Abadi 2011 [41]	Clinical study/75 cases	Pituitary function impairment after moderate traumatic brain injury
Wilkinson 2012 [38]	Clinical study/26 cases (case—control)	High prevalence of chronic pituitary and target-organ hormone abnormalities after blast-related mild traumatic brain injury
Hannon 2013 [42]	Clinical study/100 cases	Acute glucocorticoid deficiency and diabetes insipidus are common after acute traumatic brain injury and predict mortality
Baxter 2013 [39]	Clinical study/19 cases	Pituitary dysfunction after blast traumatic brain injury: the UK BIOSAP study
Ioachimescu 2015 [40]	Clinical study/20 cases	Growth hormone deficiency after mild combat-related traumatic brain injury
Giuliano 2017 [34]	Clinical study/48 cases	Growth hormone deficiency and hypopituitarism in adults after complicated mild traumatic brain injury

N.I. no information is reached

but for the medical disciplines that are required to treat such patients in, or outside, of a hospital setting. Neuroendocrine impairment following TBI is common, and it can impair the quality of life of the survivors. Hence, large prospective studies using rigorous diagnostic criteria are needed to guide clinical practice better. The best approach to the early assessment of risk following a TBI is likely to rely on pituitary swelling seen on MRI or assessment of anti-pituitary antibodies. Transient GHD may contribute to the post-concussion syndrome as well. To date, variously proposed hypotheses regarding pathological mechanisms emphasized several causes of which PTHP, and particularly GHD, are of utmost importance. Underlying pathophysiological pathways such as ischemic injury, neuroendocrine insults to the pituitary gland, and immune-related mechanisms following head trauma, frequently produce impairment in the anterior pituitary. Following TBI, pituitary volume loss without the accompaniment of PTHP were interpreted to be the result of necrosis and fibrosis. Indisputably more clinical data analysis and experimental models are needed to elucidate

the exact mechanisms behind post-traumatic pituitary damage. Finally, these studies are needed to define better the mechanisms by which PTHP occurs and the impact of neuroendocrine dysfunction following TBI. Preventive medical measures should be taken to limit possible progressive time-based damage in the pituitary gland and hypothalamic-pituitary axis in order to maintain or restore normal physiologic functions to patients affected by TBI.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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