Brain and Spine 4 (2024) 102830

Contents lists available at ScienceDirect

Brain and Spine

journal homepage: www.journals.elsevier.com/brain-and-spine

Acute neuroendocrine changes after traumatic brain injury

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ARTICLE INFO

Handling Editor: Dr W Peul

Keywords:
Traumatic brain injury
Neuroendocrine changes
Acute pituitary disfunction
Post-traumatic hypopituitarism

ABSTRACT

Introduction: Post-traumatic hypopituitarism (PTHP) is a significant, but often neglected consequence of traumatic brain injury (TBI).
Research question: We aimed to provide a comprehensive overview of epidemiology, pathophysiology, clinical features and diagnostic approaches of PTHP.
Materials and methods: MEDLINE, EMBASE, Cochrane Library and Web of Science were searched. 45 articles of human studies evaluating acute endocrine changes following mild, moderate and severe TBI were selected.
Results: Severity of TBI seems to be the most important risk factor of PTHP. Adrenal insufficiency (AI) was present in 10% of TBI patients (prevalence can be as high as 50% after severe TBI), and hypocortisolemia is a predictor of mortality and long-term hypopituitarism. Suppression of the thyroid axis in 2–33% of TBI patients may be an independent predictor of adverse neurological outcome, as well. 9–36% of patients with severe TBI exhibit decreased function of the somatotrophic axis with a divergent effect on the central nervous system. Arginine-Vasopressin (AVP) deficiency is present in 15–51% of patients, associated with increased mortality and unfavorable outcome. Due to shear and injury of the stalk hyperprolactinemia is relatively common (2–50%), but it bears little clinical significance. Sex hormone levels remain within normal values.
Discussion and conclusion: PTHP occurs frequently after TBI, affecting various axis and determining patients' outcome. However, evidence is scarce regarding exact epidemiology, diagnosis, and effective clinical application of hormone substitution. Future studies are needed to identify patients at-risk, determine the optimal timing for endocrine testing, and refine diagnostic and treatment approaches to improve outcome.

1. Introduction

Traumatic brain injury (TBI) is a significant public health problem, with an estimated annual incidence of 235 per 100,000, leading to 1.4 million emergency department visits and around 200,000 hospitalizations in European countries each year (Tagliaferri et al., 2006; National Clinical Guideline et al., 2014). The predominant causes of TBI are falls, motor-vehicle accidents, assaults, and sports-related concussions (Tagliaferri et al., 2006; National Clinical Guideline et al., 2014). There is a noticeable male predominance in these cases. Notably, in the western world the incidence of TBI is particularly high among older adults, largely attributed to an increased risk of falls and associated complications. This higher risk in older adults is further complicated by age-related physiological changes and the potential presence of multiple morbidities (Toth et al., 2021; Zhang et al., 2022; Robles et al., 2022; Amgalan et al., 2022), exacerbating the severity of TBI.

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https://doi.org/10.1016/j.bas.2024.102830
Received 4 February 2024; Received in revised form 26 April 2024; Accepted 6 May 2024
Available online 7 May 2024

The prognosis of TBI is depending on the initial severity of the injury and the effectiveness of managing secondary injuries. It is widely recognized that TBI-related neuroendocrine changes play a significant role in the long-term disability and diminished quality of life of many survivors. These changes, while varying in their manifestation and intensity, contribute to the overall impact of TBI (Park et al., 2010).

Until recently, post-traumatic hypopituitarism (PTHP) has been an often neglected and thus underdiagnosed complication of TBI. The prevalence of PTHP varies among studies due to heterogeneity of TBI severity, testing protocols and diagnostic thresholds (Kokshoorn et al., 2010; Glynn et al., 2013). The clinical presentation of PTHP is often subtle and challenging to discern, further preventing to obtain appropriate data (Caputo et al., 2019).

A meta-analysis found a pooled PTHP prevalence of 27.5% evaluated after 5 months post-injury and demonstrated a positive correlation with TBI severity (Schneider et al., 2007). Accordingly, Vos et al. showed relatively low incidence (<1%) of PTHP in mild TBI patients (van der Eerden et al., 2010).

As shown by numerous current studies (Alavi et al., 2016; Hacioglu et al., 2023; Hannon et al., 2013; Marina et al., 2015; Ntali et al., 2019), in addition to its negative long-term effects on quality of life (Ahmed et al., 2021), morbidity and mortality (Hannon et al., 2010; Hari Kumar et al., 2016), PTHP may harbor potentially life-threatening metabolic derangements during the acute phase of TBI. Accordingly, early diagnosis and appropriate hormone supplementation therapy can significantly improve outcomes (Caputo et al., 2019).

The goal of our review was to give an up-to-date and comprehensive overview of the epidemiology, pathophysiology, clinical features, and diagnosis of PTHP in the acute phase (defined as 3 months) after moderate and severe TBI, highlighting the importance of timely interventions.

2. Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P).

2.1. Literature research

A comprehensive literature research was carried out in MEDLINE, EMBASE, Cochrane library and Web of Science on the 12th of September in 2023 based on the following search term: (traumatic AND ((brain injury) OR (cerebral injury) OR (head injury))) AND ((endocrine) OR (pituitary)).

2.2. Study selection

The articles included in this review were selected based on the following inclusion criteria: all types of TBI; endocrine disorders were assessed in the acute phase of TBI (within 3 months); peer-reviewed English language full text papers are available. Studies without diagnosis of TBI; case presentations, papers that included animal data or published before 2010 were excluded.

Two independent authors separately evaluated the search results based on titles (first step), abstracts (second step) and full texts considering the inclusion criteria. In case of disagreement, a third author was involved in the decision. The references of the included full texts were reviewed to identify further relevant studies. Overall, 45 full texts were included, and data was extracted, critically reviewed, and categorized based on the assessed endocrine parameters (Fig. 1).

3. Pathophysiology of TBI-induced neuroendocrine changes

The etio-pathology of post-TBI neuroendocrine disturbances is multifaceted. From a temporal point of view, the two main contributors are the immediate effects of the initial blow and the culmination of secondary injuries (Temizkan et al., 2019).

3.1. Immediate effects of TBI

The direct mechanical insult at the time of injury may affect the hypothalamic-pituitary region, resulting in lesions in the pituitary gland, stalk, and neurosecretory hypothalamic nuclei (Kibayashi et al., 2012; Idowu et al., 2017). The pituitary stalk is especially vulnerable at the level of the diaphragm sellae in case of

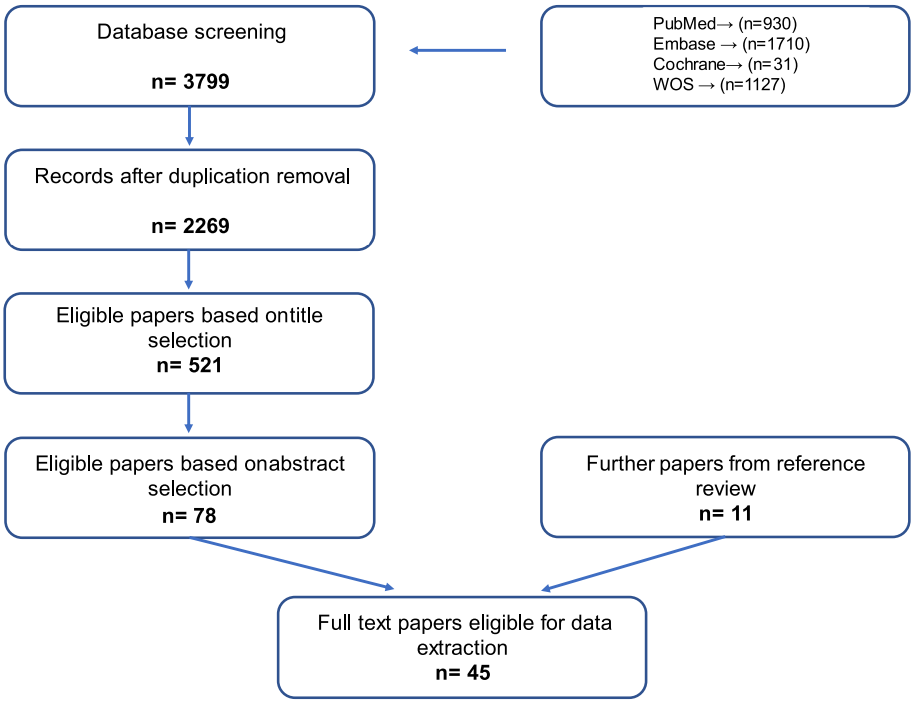

Fig. 1. Flow chart of the systematic search strategy.

acceleration/deceleration-type injuries. Pituitary lesions are often seen with fractures of the base of the skull involving the sellar region (Kibayashi et al., 2012). Most of the adenohypophysis lacks direct arterial feeders and is supplied by long portal vessels originating at the level of the median eminence (Zaben et al., 2013). The long course of these vessels renders the distal parts of the adenohypophysis particularly prone to damage during hypoxic and hypotensive episodes. Furthermore, injury of the portal vessels is frequently seen along with stalk transgression and high energy trauma (Tan et al., 2019). The most commonly affected hormones after vascular injuries are GH and gonadotrophins, likely explained by the peripheral localization of somatotrophic and gonadotrophic cells in the pituitary (Kibayashi et al., 2012). Microvascular and microstructural changes have been documented even after mild TBI, at least partly explaining the relatively high prevalence of hormonal derangements after concussion (Dusick et al., 2012; Hacioglu et al., 2019a). The causal role of vascular changes is supported by the autopsy findings of patients who sustained fatal closed head injuries. Kibayashi et al. found hypothalamic-pituitary lesions in more than 40% of autopsy cases (Kibayashi et al., 2012). Posterior lobe hemorrhage was the most prevalent finding, followed by anterior lobe infarction and hemorrhage. Supraoptic and paraventricular hypothalamic nuclei were found to be the predominant sites of hypothalamic (42%) ischemic/hemorrhagic changes. In case of stalk injury (3%), retraction balls of neurophysin (precursor of vasopressin) were observed in the hypothalamus, indicating denervation of the posterior lobe (Kibayashi et al., 2012). Interestingly, diffuse brain swelling on initial CT head scan, DAI and basal skull fracture were found to be associated with PTHP in a few studies (Schneider et al., 2007; Kelly et al., 2000), however two other studies (Bondanelli et al., 2004; Agha et al., 2004) failed to confirm this association.

3.2. Secondary injuries

Secondary injuries are considered to be a compilation of molecular processes that are initiated at the moment of trauma and continued onward to cause further (potentially preventable) brain damage (Zaben et al., 2013; Dusick et al., 2012). They include (but are not limited to) glutamate mediated excitotoxicity, neuroinflammation and secondary infarction due to hypoxia, hypotension, and microvascular occlusion (Tan et al., 2019; Dusick et al., 2012). These may impair the normal function of the hypothalamo-hypophyseal axis in various ways. Edema formation and hematoma expansion lead to increasing ICP and after depletion of compensatory mechanisms, impede blood flow in portal vessels, leading to focal ischemia, promoting excitotoxicity, oxidative stress and ultimately cell death (Dusick et al., 2012; Kalas et al., 2023).

Microglia cells play a pivotal role in neuroinflammation and can alter the hypothalamic-pituitary axis in multiple ways (Mele et al., 2021). Communication between the parvocellular hypothalamic axons and portal circulation of the pituitary occurs at the median eminence. Neuroinflammation changes permeability of tanycytes (barrier cells at the median eminence), disrupting their regulatory function of hypothalamic hormone release into the portal system (Mele et al., 2021; Osterstock et al., 2014). Increased blood-brain barrier permeability also leads to exposure of hypothalamic and pituitary antigens and subsequently the formation of anti-pituitary (APA) and anti-hypothalamic antibodies (AHA), promoting long-term autoimmune processes (Vijapur et al., 2020; Guaraldi et al., 2015; Zhang et al., 2012).

The complex pathophysiology of PTHP underlines the importance of collaborative patient care, requiring close cooperation between endocrinologists, intensive care physicians and neurosurgeons (Fig. 2).

4. Clinical presentation, diagnosis and treatment of TBI-induced neuroendocrine changes

4.1. TBI-induced changes of the hypothalamic-pituitary-adrenal (HPA) axis

Physiological steroid response after TBI plays a central compensatory role by improving hemodynamics and metabolism, while blunting excessive inflammatory reactions (Komoltsev et al., 2022; Dalwadi et al., 2017). In a number of post-TBI neuroendocrine studies, cortisol was found to be the most frequent hormone to increase and reached its peak

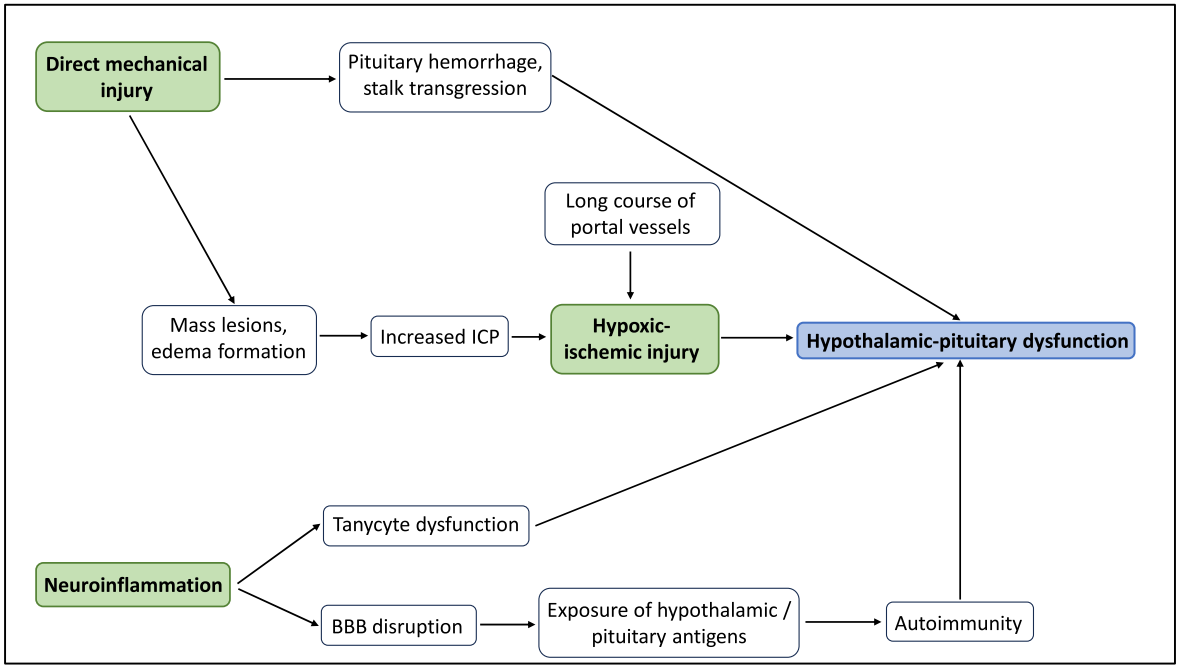

Fig. 2. Proposed mechanisms of post-traumatic hypopituitarism (PTHP) and their relationships. Mechanical injuries cause direct pituitary damage, as well as mass lesions that lead to increased ICP and hypoxic-ischemic injuries, exacerbated by the long course of portal vessels. Neuroinflammation damages tanycytes that regulate hypothalamic hormone release at the median eminence. Focal and global destruction of the blood-brain barrier exposes antigens that could trigger autoimmune reactions against the pituitary gland. BBB: blood-brain barrier.

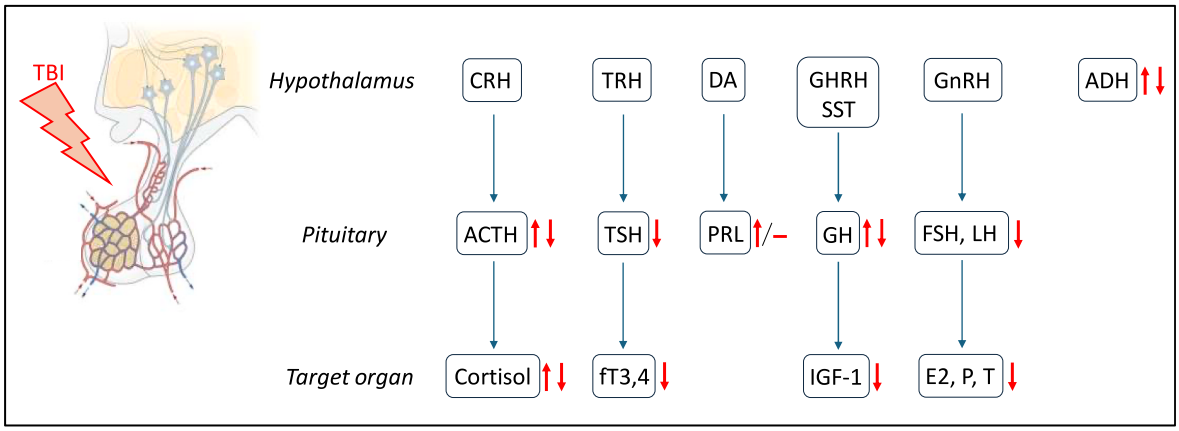

Fig. 3. Summary of endocrine changes in the acute phase of traumatic brain injury (TBI). Effects of TBI lead to various alterations in each axis of the hypothalamo-pituitary system (HPA). Derangements of the HPA axis can present as secondary hypocortisolemia as well as compensatorily elevated glucocorticoid levels. Cortisol peaked within 24 h, while adrenal insufficiency ensued during the first 10 post-injury days. Hypothyroidism is also a common feature and conveyed poor prognosis, although no clear temporal pattern was observed. If involved, prolactin production displays an increase due to disinhibition. This phenomenon can manifest within a few days after the injury and may persist up to several months in severe cases. Examination of the somatotroph axis often shows suppression within the first few days, followed by peripheral GH resistance, demonstrated by elevated GH and decreased IGF-1 levels at 3 months follow-up. As part of the stress response, gonadotrophins are usually suppressed during the first 10 post-injury days and tend to slowly normalize afterwards. Insufficient or overly active ADH production and release leads to sodium and water homeostasis imbalances, seen as AVP-D or SIADH, respectively. These derangements are usually transient and confined to the in-hospital period in the majority of cases.
TBI: traumatic brain injury, CRH: corticotropin-releasing hormone, ACTH: adrenocorticotropic hormone, TRH: thyrotropin-releasing hormone, TSH: thyroid stimulating hormone, fT3,4: free triiodothyronine, free thyroxine, DA: dopamine, PRL: prolactin, GHRH: growth hormone-releasing hormone, SST: somatostatin, GH: growth hormone, IGF-1: insulin-like growth factor 1, GnRH: gonadotropin hormone-releasing hormone, FSH: follicle-stimulating hormone, LH: luteinizing hormone, E2: estradiol, P: progesterone, T: testosterone, ADH: antidiuretic hormone.

within 24 h (Dalwadi et al., 2017; Agrawal et al., 2017; Prasanna et al., 2015). This elevation was shown to be transient at follow-up (Prasanna et al., 2015; Choudhary et al., 2023). Lower GCS entailed higher cortisol and ACTH levels, suggestive of activation of the HPA axis (Dalwadi et al., 2017). Higher cortisol levels heralded poor outcome shown by a positive correlation with severity. Beyond the effects of the injury itself, this can (at least partly) be attributed to the excessive metabolic effects of glucocorticoids at higher levels (Dalwadi et al., 2017; Choudhary et al., 2023).

There is ambiguous nomenclature in the literature of post-TBI adrenal insufficiency (AI), either simply referred to as hypocortisolemia, or – more precisely – defined as decreased ACTH and consequently lowered cortisol levels (Tan et al., 2017). Thus, care should be taken during the interpretation of prevalence data. Two recent studies have indicated high frequencies (52–78%) of HPA axis dysfunction during the first 10 post-injury days (Hannon et al., 2013; Olivecrona et al., 2013). At follow-up, 39% had at least 1 hormone deficiency, all of whom had hypocortisolemia in the acute phase. Studying 58 TBI patients, Alavi and colleagues reported low cortisol levels in 6 patients (10,3%) in the first week, with only 1 patient demonstrating features of partial ACTH deficiency (Alavi et al., 2016). In their study of 63 severe TBI patients, Nemes et al. found decreased ACTH levels in 9,5% (Nemes et al., 2016). (Table 1)

Several risk factors were identified for acute secondary adrenal insufficiency after TBI, the most apparent being the severity of injury (as per GCS and injury severity score), but younger age, skull base fractures, intraparenchymal hematoma, concurrent diabetes insipidus and medication effects (such as propofol or etomidate) were proposed, as well (Dlela et al., 2020; Chen et al., 2020).

The state of critical illness also imposes greater stress hormone demand, rendering patients prone to manifestations of corticosteroid insufficiency (Zhao et al., 2013). Olivecrona et al. reported a large proportion of severe TBI patients (54% on day 1, and 70% on day 4) with critical illness related corticosteroid insufficiency (CIRCI), defined by morning hypocortisolemia (Olivecrona et al., 2013). In a previous study, CIRCI was present in 5,6%, 22,5% and 52,2% of mild, moderate and severe TBI, respectively, and was associated with poor prognosis (Chen et al., 2020).

Table 1
Prevalence of secondary adrenal insufficiency in the acute phase after TBI in adults.

Study	*n*	*GCS*	*time from injury*	*% of patients with hypofunction of HPA axis*
Alavi et al. (van der Eerden et al., 2010)	58	<14	0–7 days	10,3
Hannon et al. (Hacioglu et al., 2023)	100	<14	1–10 days	78
Olivecrona et al. (Agrawal et al., 2017)	45	<9	1 day	54
			4 days	70
Krahulik et al. (Choudhary et al., 2023)	186	3–14	“acute”	10

TBI: traumatic brain injury, GCS: Glasgow coma scale, ACTH: adrenocorticotropic hormone.

Impairment of the hypothalamus-pituitary-adrenal (HPA) axis should be acknowledged as the most significant neuroendocrine disturbance during in-hospital care after TBI. The potentially life-threatening hemodynamic and metabolic consequences of hypocortisolemia make appropriate diagnosis and timely intervention important. In case of pressor-resistant hypotension, hypoglycemia and hyponatremia, suspicion of AI should be raised. After blood sampling for random cortisol measurement, empirical treatment with hydrocortisone (50 mg every 6 h intravenously, or 50–100 mg as an initial iv bolus followed by an infusion rate of 4–8 mg/h) should be started (Tan et al., 2017). In order to obviate the potentially deleterious consequences of adrenal insufficiency, Tanriverdi and colleagues proposed that all TBI patients should have morning cortisol levels checked on the 1st-4th days of neuro ICU stay regardless of clinical suspicion (Tanriverdi et al., 2011).

Since insulin tolerance testing carries the risk of provoked seizures in brain injured patients and the glucagon test has shown high rates of false

positivity, diagnosis of AI is confined to the clinical picture and measurement of serum/plasma cortisol and ACTH (Hannon et al., 2013). In the studies reviewed here, sampling for cortisol measurements was generally done in the morning to comply with diurnal fluctuations. Interestingly, circadian variability of cortisol seemed to be lost in both serum and cerebral microdialysis samples during the first 5 days in a study of patients with moderate to severe TBI (Llompart-Pou et al., 2010). Also, amplitude of diurnal fluctuations in salivary cortisol was also proposed to be a biomarker for TBI severity and neurobehavioral impairment in a current study (Villegas et al., 2022).

In most studies, cut-off values for hypocortisolemia in plasma and serum samples were accepted as 276 nM (10 μg/dl) and 300 nM (11 μg/dl), respectively, and secondary AI was considered under an ACTH value of 9 pg/ml (Olivecrona et al., 2013; Chen et al., 2020). When available, a combination of basal cortisol level and cosyntropin stimulation testing (either with a dose of 1 or 250 μg) can improve diagnostic certainty, with diminished responses (an increase of <9 μg/dl in cortisol levels) indicating AI (Mirzaie et al., 2013).

The clinical picture of hypotension, hyponatremia and hypoglycemia may increase the risk of morbidity and mortality. In numerous studies, AI – especially if lasting beyond the acute period – was a predictor of mortality and long-term hypopituitarism in TBI (Hannon et al., 2013; Ntali et al., 2019; Dlela et al., 2020; Bensalah et al., 2018). The predictive power of cortisol is further supported by the findings of Kumar et al., who demonstrated positive correlation between mean cortisol on day 4 and survival at 3 months (Vishwa Kumar et al., 2021).

On the contrary, in a cohort of severe TBI none were supplemented with glucocorticoids, yet no correlation could be observed between low cortisol levels and unfavorable outcome or increased mortality on 3 months follow-up (Olivecrona et al., 2013). Recovery of hypocortisolemia was observed in 50% of patients in the same study.Fig. 3

4.1.1. Pediatric aspects

Along with adults, head trauma is also common in childhood, making it the leading cause of death and acquired disability in children. In recent years, increasing number of papers has been published on hormonal changes caused by TBI in children (Jourdan et al., 2012). In the acute stage (first 24 h), Ulutabanca et al. documented 44,3% of patients to have at least one pituitary hormone dysfunction (Ulutabanca et al., 2014).

There is limited evidence in the context of adrenal hormonal changes after TBI in the pediatric population. In a prospective study of 41 traumatic brain injured children (ranging from mild to severe) 24,4% had ACTH deficiency in the acute phase, all of which subsided by 12 months (Ulutabanca et al., 2014). Transient changes suggest an adaptive physiologic response; thus, prevalence of acute hormonal defects cannot be translated to chronic deficiencies. Krahulik et al. also found supposedly physiological elevations of cortisol and ACTH during the first two weeks in 10% of children after moderate to severe TBI (Krahulik et al., 2017). In a study applying high frequency sampling of cortisol and ACTH between the morning of 2nd and 3rd post-injury days, 36% of patients were found to have secondary adrenal insufficiency, with hypocortisolemia being more frequent in the group of patients with intracranial hypertension (Dupuis et al., 2010).

4.2. TBI-induced changes of the pituitary-thyroid axis

It is generally believed that thyroid function, particularly the serum levels of free triiodothyronine (fT3), thyroid-stimulating hormone (TSH), and free thyroxine (fT4), may act as prognostic indicators following TBI (Dupuis et al., 2010). A commonly recognized phenomenon is thyroid axis suppression in TBI patients, typically defined by reduced fT4 levels and low or inappropriately normal TSH concentrations. This suppression is often seen as an independent predictor of patient outcomes. Nevertheless, the specific dynamics of these hormonal changes and their clinical significance remain somewhat unclear and are occasionally subject to debate.

In a study by Mele et al., involving 243 mild-to-severe TBI patients, a significant relationship was found between elevated TSH, reduced fT3, and adverse neurological and functional outcomes (Mele et al., 2022). Dalwadi et al. noted a correlation between lower fT3 and fT4 levels and the severity of TBI, linking reduced fT3 to higher mortality, suggesting its potential as a risk marker of mortality (Dalwadi et al., 2017). In another study (Agrawal et al., 2017), pituitary-thyroid axis was affected with a decrease in fT3 and fT4 levels. Moreover, a significant correlation was observed between fT4 levels at 30 days and Glasgow Coma Scale scores at discharge. They showed that hormone replacement therapy made a positive impact on patients outcome, especially in improving Glasgow Outcome Scale scores.

In contrast, studies by Hannon et al. and Jonasdottir et al. reported no significant hormonal changes in the pituitary-thyroid axis in TBI patients (Hannon et al., 2013; Jonasdottir et al., 2018).

The timing of these hormonal alterations varies across studies. Some studies show central hypothyroidism developing within 6 months post-TBI (Krahulik et al., 2010). While others note its presence immediately after the injury in the acute phase (Hari Kumar et al., 2016; Prasanna et al., 2015). Notably, this condition was found to be often transient. 85% of patients experienced spontaneous recovery. Also, critical illness from TBI could induce a biphasic neuroendocrine response: initially marked by elevated catabolic and decreased anabolic hormone levels, followed by a suppression of hormone secretion like TSH (Mazzeo et al., 2019).

Further evidence highlights the dynamic changes of thyroid hormones after TBI. Specifically, lower levels of TSH, fT4, and fT3 observed on day 4, especially with the absence of increasing trends in these hormones were linked to poorer outcomes (measured by the Glasgow Outcome Scale) at 3 months (Vishwa Kumar et al., 2021). Hormonal fluctuations over a six-month period post-TBI were also observed, with a noted trend of decreasing T3 and T4 levels (Choudhary et al., 2023). Zheng et al. also explore dynamic changes in pituitary hormones after TBI, finding a correlation between lower levels of FSH, testosterone, GH, fT3, and fT4 and poor neurological outcome (Zheng et al., 2014). These observations support the argument that continuous monitoring of hormone levels could be vital in predicting patient outcome and tailoring post-TBI management strategies.

Additionally, Nemes et al. suggest that although most pituitary deficiencies typically resolve over time, a significant proportion remains even one month after the injury. This underscores the importance of regular endocrine screening in patient management (Nemes et al., 2016).

Collectively, these studies form a body of evidence suggesting that TBI induces significant alterations in thyroid and other hormone levels, which can serve as important indicators of injury severity and predictors of recovery and long-term neurological outcome. The consistent observation across studies of the prognostic value of thyroid hormone levels post-TBI underscores the potential utilization of these hormones as biomarkers. It also suggests that regular screening and appropriate hormonal supplementation could play a vital role in patient management and rehabilitation following TBI.

4.2.1. Pediatric aspects

Out of 414 pediatric patients with moderate-to-severe TBI, 33 had abnormal TSH levels, with the majority (78.8%) of these patients having high TSH. This abnormal elevation in TSH could act as an early indicator of the severity of head trauma, sometimes referred to as ‘pituitary concussion’ and might be associated with a poorer prognosis. Similar to adults, a higher incidence of TSH abnormalities was noted in female patients, possibly linked to the natural hormonal fluctuations in female physiology (Aggarwal et al., 2020).

4.3. TBI-induced changes of the somatotrophic axis

The GH/IGF-1 axis, critical for neuroprotection and vascular health, is frequently disrupted following TBI. This vulnerability primarily stems from the anatomical positioning of somatotrophic cells within the pituitary gland. These cells, situated peripherally and nourished by long, winding portal vessels, are particularly susceptible to ischemic damage (Kibayashi et al., 2012). In terms of prevalence, on average, 18% of patients with acute severe TBI exhibit some level of somatotrophic axis dysfunction (Olivecrona et al., 2013). However, variability exists; Krahulik et al. reported a higher prevalence, finding dysfunction in 37% of acute TBI cases, with the majority showing recovery by three months (Krahulik et al., 2010). Interpretation of these findings necessitates caution due to the heterogeneity in study designs, including diverse inclusion criteria, diagnostic tests, and threshold values. A study conducted by Gandhi et al. highlighted that decreased GH levels were evident in 28% of acute TBI patients on the first day, escalating to approximately 49% by the seventh day (Prasanna et al., 2015).

The anti-aging and neuroprotective roles of pituitary-derived GH and liver-produced IGF-1 are well-established (Sonntag et al., 2005, 2013; Mitschelen et al., 2011; Dabin et al., 2022; Ashpole et al., 2017). These hormones are also pivotal in maintaining the integrity and function of the cardiovascular and cerebrovascular systems (Bickel et al., 2023; Napoli et al., 2003; Scheepens et al., 2001; Silha et al., 2005; Tarantini et al., 2021a, 2021b; Norling et al., 2020; Kiss et al., 2022; Wagner et al., 2010). GH and IGF-1 receptors are abundantly present throughout the central nervous system (CNS), mediating a range of critical functions. These include regulating endothelial function and vascular reactivity, ensuring proper neurovascular coupling (Toth et al., 2022) and autoregulation (Toth et al., 2014), and facilitating repair mechanisms. IGF-1, in particular, is integral to brain function, contributing to neuronal growth, cell proliferation, and autophagy, a process crucial for the removal of damaged organelles and the maintenance of cellular function. Aging significantly impacts the GH/IGF-1 axis, typically characterized by a decline in the production and sensitivity to these hormones. This reduction is associated with various physiological changes, including decreased muscle mass and strength, reduced cognitive function, and impaired vascular health. Clinical and experimental studies demonstrate that diminished GH/IGF-1 axis contributes to generalized vascular dysfunction (Bickel et al., 2023), characterized by increased microvascular fragility and genesis of cerebral microhemorrhages (Tarantini et al., 2017; Miller et al., 2022), BBB disruption, impaired angiogenesis and microvascular rarefaction (Sonntag et al., 2013; Tarantini et al., 2016), pathological remodeling (Fulop, 2018), endothelial dysfunction and dysregulation of cerebral blood flow (Toth et al., 2015) and a general decline in vascular repair mechanisms. These changes, combined with impaired function of neurons and astrocytes are causally linked to cognitive decline (Zhang et al., 2022; Toth et al., 2022; Kerkhofs et al., 2021; Bakhtiari et al., 2023; Fan et al., 2021; Montagne et al., 2022; Towner et al., 2021; Gulej, 2023; Vestergaard et al., 2022; Fang et al., 2022; Tarantini et al., 2021c; Sabayan et al., 2021; Verheggen et al., 2020).

The neuroprotective and vasculoprotective effects of GH/IGF-1 signaling are thought to be critical for the preservation of cognitive function also in the context of TBI. Accordingly, reduced plasma IGF-1 levels have been correlated with cognitive impairments in TBI patients (Arwert et al., 2005; Feeney et al., 2017). In a TBI animal model, research by Ping et al. demonstrated that overexpression of astrocytic IGF-1 could improve cognitive dysfunction and mitophagy, which is crucial for cellular function maintenance (Dabin et al., 2022).

Various patterns of alterations can be observed in the somatotrophic axis in the acute phase of TBI, largely irrespective of age. Generally speaking, the cooccurrence of decreased IGF-1 and elevated or decreased basal GH levels can be interpreted as a state of acquired peripheral GH resistance (Mazzeo et al., 2019). An acknowledged hypothesis suggests that suppression of the secretion of anabolic hormones (including GH) results in decreased energy consumption and the preservation of metabolic resources essential for sustaining vital organs (Tan et al., 2017; Preiser et al., 2014). This repression is induced by the stress response and is likely an adaptive mechanism since exogenous GH administration increased mortality in a study of critically ill patients (Mazzeo et al., 2019). More severe injuries entailed higher anabolic suppression by stress hormones, resulting in lower IGF-1 levels (Preiser et al., 2014). It is also important to emphasize that this pattern is commonly observed in extracranial trauma and critical illness and is not a TBI-specific phenomenon (Mazzeo et al., 2019).

Interpretation of data regarding somatotrophic axis deficiency is difficult not only because of the heterogeneity of studies, but also due to some inherent properties of the physiology of this system. The pulsatile nature of GH secretion produces great variability in GH levels if measured only once daily (as was the case in almost all studies). In studies that used multiple daily sampling there was no diurnal pattern observed in the secretion of GH. These issues warrant high frequency sampling in future studies. Some drugs commonly used in ICUs (especially Clonidine and Metoprolol) may increase GH secretion, leading to false results (Olivecrona et al., 2013). GH and IGF-1 values are also influenced by nutritional and hormonal status. Additionally, body mass index (BMI) has been noted to influence both GH and IGF-1 levels, with IGF-1 decreasing in cases of very high or low BMI (Fleseriu et al., 2016).

Wagner et al. examined GH and IGF-1 levels each day for 10 days post-TBI. Their findings indicate that transient somatotroph suppression occurs in over 75% of TBI patients. A tendency towards normal levels in both GH and IGF-1 were observed during the first 10 post-injury days. Moreover, 26% of TBI patients demonstrated elevated IGF-1 levels at 3 months follow-up (Wagner et al., 2010). As showed by a recent study, patients with moderate and severe TBI experienced a more lasting decrease in GH levels (5% had low GH levels at 6 months), while those with mild TBI experienced a return to normal levels as early as one month post-injury (Zheng et al., 2014). Another study that examined hormone levels only on the first post-injury day, observed low IGF-1 levels in 46.9% of patients, but they could not demonstrate its correlation with severity. Patients with severe TBI exhibited higher GH levels compared to those with mild TBI (Dalwadi et al., 2017). This discrepancy might be attributed to increased GH resistance in individuals with more severe TBI. A recent study revealed that GH levels post-TBI varied depending on the treatment approach, with generally lower levels in patients receiving conservative treatment compared to those undergoing surgery (Choudhary et al., 2023).

Given their robust neuroprotective effects, alterations in the somatotrophic axis could have significant implications for patient outcome following TBI. Research efforts have been directed at assessing the predictive value of GH and IGF-1 levels for TBI outcomes, yet the findings have been inconsistent. For instance, Dalwadi et al. observed that, within the first 24 h post-admission, IGF-1 levels did not show a clear relationship with the severity of the injury. However, they noted elevated GH levels in cases of severe TBI, suggesting an increased resistance to GH in these more critical conditions (Dalwadi et al., 2017). Interestingly, there was an observed trend, although not statistically significant, linking lower initial GH levels with poorer outcome on the Glasgow Outcome Scale (GOS) at a 3-month follow-up. Conversely, Olivecrona et al. reported no significant association between initial GH levels and various outcome measures, including the Glasgow Coma Scale (GCS), GOS, maximum intracranial pressure (ICP_{max}), minimum cerebral perfusion pressure (CPP_{min}), Injury Severity Score, or Marshall score (Olivecrona et al., 2013). This variability in findings underscores the complexity of the GH/IGF-1 axis in TBI and highlights the need for further, more nuanced research to elucidate its role in TBI prognosis.

4.3.1. Pediatric aspects

Retrospective investigations of TBI have identified neuroendocrine dysfunction in 15–21% of children. In the acute phase, Krahulik et al. found 8,62% of patients to have decreased levels of IGF-1. Within a

cohort of 58 children and adolescent survivors of head trauma, two boys with severe TBI and a combined deficiency of pituitary hormones (GH, TSH and ACTH) were observed (Krahulik et al., 2017). The occurrence of endocrine dysfunction at early stage exhibited a significant correlation with the severity of the injury. Key indicators of GH deficiency in pediatric patients include decelerated growth rate and delayed bone maturation (Ranke, 2021). BMI assessments conducted monthly revealed initial weight loss followed by a rapid increase in weight post-TBI. Notably, male sex was identified as a risk factor for excessive weight gain in the pediatric population following TBI (Barlow, 2012).

4.4. TBI-induced changes in prolactin production

Hyperprolactinemia occurs in more than 50% of TBI survivors in the early, acute phase (Prasanna et al., 2015; Choudhary et al., 2023). The serum prolactin (PRL) level measured on the first day after TBI showed a significant negative relationship with cerebral perfusion pressure (CPP_{min}) and a positive correlation with intracranial pressure (ICP_{max}), each of which could be a prognostic factor of clinical outcome. This was confirmed by other studies showing that PRL levels correlate with severity of TBI (Dalwadi et al., 2017; Prasanna et al., 2015; Zheng et al., 2014).

This is consistent with the results of Zheng et al., who found elevated PRL levels in the acute stage in severe TBI cases. On the 28th day after the injury, a decrease was observed in those with mild brain injuries, while the PRL levels continued to rise in the group of moderate and severe TBI (Zheng et al., 2014). In a study examining 111 TBI patients who underwent neurorehabilitation, the phenomenon of hyperprolactinemia is also described: elevated PRL levels were measured in 49% of the patients three months after the head injury (Marina et al., 2015). The processed studies also included those that reported milder changes or unchanged PRL levels. In a study of 100 moderate-to-severe head injured patients by Choudhary et al., hyperprolactinemia was seen in 15 patients at day 2, while in 85% of patients the serum PRL levels were in normal range. The PRL level was low in the conservative group as compared to the surgical group and was high in severe TBI cases (Choudhary et al., 2023). Kumar et al. found that mean serum PRL was found to be within the normal range both on day 1 and day 4, and there was no statistically significant difference between the deceased and survivors, and PRL levels were not correlated to GCS. Their study has revealed that serum PRL on day 1 or day 4 did not predict survival or outcomes in their 54 patients with history of severe TBI (Vishwa Kumar et al., 2021).

These results are confirmed by the findings of Jonasdottir et al., who describe low PRL levels in 2 out of 12 moderate-to-severe brain injured patients, while none of the patients were hyperprolactinemic. Also, in contrast to the reports of previous studies, who found high percentage of hyperprolactinemia, Prasanna et al. found only 6 out of 100 patients (52 moderate, 48 severe TBI) to be hyperprolactinemic (6% on day 1 reduced 4,25% on day 7). This study found positive correlation between PRL and severity of traumatic brain injury (Prasanna et al., 2015). They also report milder changes in the results of an Indian study, where 4% of patients had an increase in PRL levels, which was negatively correlated with GCS scores, which may represent stress response to TBI (Dalwadi et al., 2017). This is supported by the finding of a study that demonstrated hormonal abnormalities following traumatic subarachnoid hemorrhage (SAH). In their study hyperprolactinemia occurred in 2.08% in groups of patients with endocrine disturbances with no hormonal replacement and 2% in replacement therapy group (Agrawal et al., 2017). Kumar et al. reported unchanged PRL levels: none of the patients had altered PRL levels in their prospective study of 56 TBI patients (Hari Kumar et al., 2016).

Collectively, alterations in the PRL hormone, particularly hyperprolactinemia, are common occurrences in the acute phase of traumatic brain injury. Upon reviewing the results, it appears to be correlated with the severity of the injury and may even possess prognostic value.

4.5. TBI-induced sex hormone deficiency

Numerous retrospective studies have highlighted that TBI mediated sex hormone abnormalities could be more frequent than previously recognized. Gonadotrophins (follicular stimulating hormone (FSH) and luteinizing hormone (LH)) and testosterone (in male patients) are commonly affected and extensively studied. Additionally, estradiol and progesteron are also examined in several research papers in female head injured patients, in particular for their supposed neuroprotective effects (Wagner et al., 2011; Ham et al., 2015).

4.5.1. Gonadotrophins

All the studies included reviewed reported deficiencies in LH and FSH. The gonadotrophins, as previously indicated, are susceptible to THE impact of TBI. This vulnerability is due to the lateral position of the producing cells within the vascular watershed territory of the hypophyseal portal system (Ham et al., 2015). Wagner et al. reported gonadotrophin suppression in a study that enrolled 101 TBI patients. According to their results, LH and FSH had similar pattern of decline over the 10-day post-injury period. Out of 101 TBI patients, LH suppression was observed in 83%, FSH in 63%. In addition, they attempted to identify factors that may be associated with gonadotropin suppression. Younger age was associated with FSH suppression: in patients under 40 years of age, a significant majority (58%) had low FSH levels, compared to only 26% in male and premenopausal female patients over 40 years of age. Their multivariate analysis did not reveal any predictive factors of LH suppression (Wagner et al., 2010). This is in line with the findings of Olivecrona et al., who found a strong suppression of pituitary-gonadal axis in the early phase after severe TBI. The levels of LH and FSH were low in the acute stage after sTBI and decreased further from day 1 (52%, 10,3%) to day 4 (58%, 37,9%), in male patients. LH and FSH levels measured on day 1 after trauma were higher in people who died within three months after the injury than in survivors, and these levels were negatively correlated with GOS scores in a third month follow up period. Furthermore, higher Marshall CT scores were associated with higher day 1 LH/FSH levels. There was a significant relationship between impairment of the pituitary-gonadal axis and outcome 3 months after severe head injury in male patients (Olivecrona et al., 2013). These findings suggest that severe traumatic brain injury causes suppression of pituitary-gonadal axis which is a poor prognostic sign (Olivecrona et al., 2013; Wagner et al., 2010).

Wagner et al. found significant sex differences for day 0 LH and FSH values after a traumatic event. Hormone levels were higher in women after TBI history than in premenopausal females without trauma. In contrast, in men LH and FSH levels were not different from the control group. However, LH and FSH levels decreased through the first 6 days after TBIand became significantly lower than in healthy subjects (Vishwa Kumar et al., 2021). Zheng et al. also found deficiency of gonadotrophins after TBI. According to their results, LH level was much higher in severe (GCS 3–8) TBI patients, as compared to mild and moderate cases at 2 weeks post injury. FSH levels also increased dramatically in the sTBI group, as compared to other groups on day-1. During the first 28 days in sTBI patients, there was a progressive decline in FSH levels (Zheng et al., 2014). Krahulik et al. also identified gonadotropin dysfunction in 33% of patients with TBI (Krahulik et al., 2010). Consistent with this, Marina et al. also found suppressed gonadal function in 32% of patients three months after severe TBI (Marina et al., 2015). In their prospective single-centre study of 27 patients from Icelandic Jonasdottir et al. reported that gonadotropin deficiency was the most common deficiency at 3 months after TBI or SAH (Jonasdottir et al., 2018). Agrawal et al. also reported low-hormone levels of gonadotropins on day 1 in patients with traumatic subarachnoid hemorrhage. These values showed a decreasing trend at day 7th, then two-weeks and one-month follow-up. According to their results, gonadotrophic hormone deficiency could be transient in the early period after TBI, which is why close follow-up is warranted (Agrawal et al.,

2017). Choudhary et al. found association between LH and outcome: serum LH levels correlated positively with third months GOS score and GCS at 2 weeks (Choudhary et al., 2023). Measurement of basal hormone levels only once per day can lead to false positive or negative results. Reliable measurments in future studies should be done with higher sampling frequency (Olivecrona et al., 2013; Wagner et al., 2010).

4.5.2. Testosterone

Wagner et al. reported low testosterone levels in 100% of the 101 traumatic brain injury patients, which persisted over the observation period (during the first 9 days). The lower levels of this sex hormone in the acute phase may exert a potential neuroprotective effect. For example, both androgens and estrogen are able to prevent cell death (Wagner et al., 2010). Interestingly acute anemia correlated with low testosterone values (Wagner et al., 2010). Olivecrona et al. also documented the suppression of the pituitary-gonadal axis in the acute phase after severe TBI. Total testosterone levels of male TBI patients were low (4.9 ± 0.9 nmol/L) at day 1 and decreased significantly to day 4 (1.4 ± 0.2 nmol/L). Testosterone levels measured on the first day post injury were significantly lower in patients who did not survive to the third month, and this level also correlated negatively to GOS scores at three months. (Olivecrona et al., 2013).

Interesingly testosterone levels in head-injured woman were higher than in control patients, which showed a decreasing trend in the first six days after the traumatic event (Wagner et al., 2011). Zheng et al. reported correlations of testosterone with the severity of TBI. In their prospective study, which enrolled 164 TBI patients of all severity, they found decreased testosterone levels in the group with GCS≤12. Furthermore, sex hormone levels recovered to normal range only in patients with history of mild TBI at one month post injury (Zheng et al., 2014).

In accordance with previous studies, Agrawal et al. reported decreasing trend in testosterone levels in male patients with traumatic subarachnoid hemorrhage, during the first month (Agrawal et al., 2017). Interestingly, Bentley et al. observed a rapid onset of disruption of gonadal androgen synthesis in patients with a mean injury severity score (ISS) of 16. They demonstrated that testosterone and 5α-dihydrotestosterone (DHT) decreased within 60 min after trauma (Bentley et al., 2023).

In contrast, a study that enrolled 100 moderate-to-severe TBI patients reported normal value of testosterone in 80 patients (89,89%), while only nine patients (10,11%) had low levels (Choudhary et al., 2023). This is in line with the findings of Dalwadi et al. who reported no significant differences in testosterone levels of survivors or deceased TBI patients, and found no significant correlation between testosterone level and GCS (Dalwadi et al., 2017).

4.5.3. Progesterone and estradiol

Experimental studies on TBI proposed the neuroprotective influences of female sex steroids on secondary mechanisms of TBI (Wagner et al., 2011). Estrogen and progesterone were shown to exert neuroprotective effects through their influence on various signaling pathways, including those that alter astrocytic and microglial functions, regulate inflammatory responses, modulate cerebral blood flow and metabolism, and dampen glutamate excitotoxicity. (Brotfain et al., 2016). Wagner et al. reported higher day 0 progesterone levels in male TBI patients, compared to healthy subjects. I contrast, day 0 progesterone levels of brain-injured women showed no difference from that of healthy premenopausal control subjects in the luteal-follicular phase of their cycle. By the 6th post-TBI day, serum progesterone levels declined dramatically. The first measured estrogen level (day 0) was significantly higher in head-injured men, compared to the healthy controls. Although not as dramatically as in the case of progesterone, estrogen levels showed a decreasing trend: by day 6 hormone levels of both men and women with TBI were low (Wagner et al., 2011). Wagner et al. also documented a reduction of estradiol value in the acute stage of TBI. According to their results, 43% of menopausal women had at least one low estradiol value, and 39% of all values were low (Wagner et al., 2010). However, other studies examining moderate-to-severe TBI patients reported less pronounced hormonal changes. Choudhary et al. found normal estrogen levels in all patients initially, but one patient had decreased levels at 2 weeks. Similar results were obtained for progesterone, with only one patient experiencing lower levels on the second day after TBI (Choudhary et al., 2023).

4.5.4. Pediatric aspects

In the study of Ulutabanca et al. out of 41 children (mean age 7 ± 4,3) 3 patients (7,3%) had high PRL levels. Only one patient exhibited low gonadotrophic hormone levels. Different results from adult measurements are probably explained by different activity of gonadotrophic hormones in children with mini puberty, prepuberty and puberty (Ulutabanca et al., 2014). Krahulik et al. deonstrated that severity of TBI determines the onset of gonadotropin dysfunction (Krahulik et al., 2017). In contrast tot he previously mentioned studies Jourdan et al. found no dysfunction in the gonadotrophic axes in children after TBI (Jourdan et al., 2012). Temporary hormonal changes during the acute period after TBI are completely restored, suggesting that these changes are likely part of an adaptive response (Ulutabanca et al., 2014).

4.6. TBI-induced neurohypophyseal dysfunction

Posterior pituitary dysfunction after TBI can lead to insufficient arginine vasopressin (AVP) release and AVP deficiency (AVP-D - formerly called central diabetes insipidus) or causes syndrome of inappropriate ADH secretion (SIADH) due to uncontrolled release of AVP.

4.6.1. AVP-D

Prevalence of AVP-D during the acute phase varies widely (15–51%) which may be attributed to clinical factors confounding the diagnosis (eg. treatment of hypovolemia by aggressive fluid replacement) (Hannon et al., 2013; Gempeler et al., 2020; Tudor et al., 2019). A more recent study of 317 patients with severe TBI identified Abbreviated Injury Scale (AIS) score of the head, intracerebral hemorrhage, subdural hematoma, and skull base fracture to be significant risk factors for AVP-D (Gempeler et al., 2020). According to current studies, the median day of onset varies between the 1st and 12th post-injury days (Hannon et al., 2013; Gempeler et al., 2020; Tudor et al., 2019). (Table 2)

In case of AVP deficiency, insertion of aquaporin-2 water channels into the luminal membrane of the collecting duct is diminished. Therefore, patients display hypotonic polyuria, subsequent hypernatremia, and increased serum osmolarity that induces polydipsia. In a minority of patients with stalk transgression, a characteristic triphasic response can be observed (Goel et al., 2018). At first, due to AVP deficiency, a polyuric phase is present for 3–6 days, which then shifts to uncontrolled release of AVP from degenerating neurons, producing a

Table 2
Prevalence of posterior pituitary dysfunction in the acute phase of TBI in adults.

Study	*n*	*Severity of TBI (GCS)*	*% of posterior pituitary dysfunction*
Gempeler et al. (Barlow, 2012)	317	≤8	14,82 (AVP-D), 2,52 (SIADH)
Hannon et al. (Hacioglu et al., 2023)	100	≤13	51 (AVP-D)
Hadjizacharia et al. (Bentley et al., 2023)	436	3–15	15 (AVP-D)
Agha et al. (Brotfain et al., 2016)	50	≤13	26 (AVP-D), 14 (SIADH)
Lohani et al. (Gempeler et al., 2020)	40	3–15	12,5 (SIADH)

TBI: traumatic brain injury, GCS: Glasgow coma scale, AVP-D: arginine vasopressin deficiency, SIADH: syndrome of inappropriate ADH secretion.

SIADH-like clinical picture for several days. After the depletion of ADH, polyuria ensues again.

In a study of 100 moderate to severe TBI patients, only 21% were found to have non-recovering AVP deficiency during in-hospital stay (Hannon et al., 2013). This proportion is corroborated by the findings of Gempeler et al., demonstrating a transient course in 80% of AVP-D patients surviving up to discharge (Gempeler et al., 2020).

Timely diagnosis of AVP deficiency is of paramount importance, due to the exacerbation of secondary injury as a result of hypovolemia, as well as its association with increased mortality and unfavorable outcome (Hannon et al., 2013; Krahulik et al., 2010; Gempeler et al., 2020). In case of polyuria and hypernatremia (although sodium levels are often in the high-normal range), suspicion for AVP deficiency should be raised. Evaluation of serum electrolytes, creatinine, glucose, simultaneous plasma and urine osmolality aids in establishing the diagnosis and excluding other etiologies of polyuria. The diagnosis is confirmed by relatively hypo-osmolar (<300 mOsm/l) basal urine output which responds to administration of desmopressin (10ug by nasal insufflation) by rising at least 15% and reaching an osmolarity of 300 mOsm/l (Temizkan et al., 2019).

Owing to the oftentimes transient nature of AVP deficiency, the administration of desmopressin (0.1–0.2 mg orally or 5-10ug by nasal insufflation) should be carried out in an on-demand manner (Tan et al., 2017). Ongoing desmopressin therapy requires close monitoring of sodium levels and fluid balance and should be used with caution in case of raised ICP, in order to prevent inadvertent fluid shifts into the brain parenchyma.

4.6.2. SIADH

The incidence of SIADH in the acute phase ranges from 2,5%–14% (Tudor et al., 2019; van der Voort et al., 2020). Characterized by excessive release of ADH, it results in euvolemic hyponatremia due to natriuretic compensatory mechanisms triggered by volume expansion.

Post-TBI hyponatremia – seen most commonly during the first post-injury week – has multifactorial etiology (Hacioglu et al., 2019b, 2023; Dutta et al., 2021). Adr enal insufficiency, impaired renal function, water overload and hypothyroidism should all be excluded or corrected before the diagnosis of SIADH is made. After confirming euvolemia, plasma hypo-osmolarity (<270 mOsm/l), paired with a urine osmolarity of at least 100 mOsm/l and urine sodium of greater than 40 mmol/l are consistent with SIADH.

Cerebral salt wasting – differentiated from SIADH only by evidence of volume depletion – was shown to be a rare entity, being sparsely reported in recent papers (Tudor et al., 2019; Cuesta et al., 2016; Ruiz-Gines et al., 2019).

The transient course of SIADH was demonstrated in a number of recent studies. Agha et al. had reported only 1 of 13 patients who had persisting symptoms, while Hannon et al. had reported none (Hannon et al., 2013; Agha et al., 2005).

To maintain cerebral perfusion and obviate complications related to hyponatremia-induced brain swelling, replenishment of sodium in post-TBI hyponatremic patients should be carried out with hypertonic (3%) saline regardless of the etiology (Cuesta et al., 2016).

4.6.3. Pediatric aspects

Data regarding acute posterior pituitary dysfunction after TBI in children is scarce. Krahulik et al. examined the course of neuroendocrine disturbances in 58 children and adolescents with moderate to severe TBI and found AVP-D in 20,7% and SIADH in 6,9% (Krahulik et al., 2017). AVP-D and SIADH were significantly more common amongst severe (11/23) vs. moderate (4/35) TBI patients. In accordance with findings in adult studies, incidence of endocrine dysfunction significantly correlated with the severity of injury. As for the treatment of AVP-D, children should follow careful fluid intake restrictions to prevent hyponatremia. Dosing of desmopressin matches the aforementioned regime, applying the lower value (daily dose of 0,1 mg orally and 5 μg intranasally) in children up to 12 years of age (Tan et al., 2017).

5. Conclusions and future directions

Although many aspects of PTHP have been elucidated in recent years, there are several uncertainties left regarding the pathophysiological mechanisms, indications for testing, diagnostic cut-off values and protocols for hormone replacement.

As for the screening, it remains unclear which patient groups should be tested for pituitary insufficiency. A higher incidence of PTHP has been observed in patients with severe TBI, necessitating a multifaceted risk stratification system to accurately identify those at risk. Such a system would incorporate assessments of injury severity, specific biomarkers, neuroimaging results, genetic predisposition, and clinical symptoms. Key biomarkers for evaluation could include pituitary hormones like adrenocorticotropic hormone (ACTH), growth hormone (GH), prolactin (PRL), thyroid-stimulating hormone (TSH), as well as their downstream effectors such as cortisol, IGF-1 and T3,4, along with antibodies targeting the hypothalamic-pituitary axis. This comprehensive approach aims to facilitate early identification of PTHP, allowing for timely investigation and intervention. In addition, the diagnostic uncertainty is complicated by the substantial overlap between endocrine and non-hormonal symptoms in TBI patients, further emphasizing the importance of targeted diagnosis.

Static blood sampling offers poor temporal resolution in hormonal evaluation, necessitating dynamic hormone analysis and high frequency sampling.

Current treatments for PTHP involve various hormone replacement therapies such as desmopressin administration and cortisol supplementation. Research is ongoing in more targeted hormonal treatment protocols, gene therapy, and administration of neuroprotective agents to improve PTHP. One interesting example to this is recombinant human GH administration, which – owing to its neuro- and vasculoprotective effects – ameliorated several outcome measures in TBI patients in a number of recent studies (Mossberg et al., 2017; Maric et al., 2010; Gardner et al., 2015). A large descriptive study is warranted in the future that incorporates the above-mentioned risk stratification system and dynamic hormone profiling to define prevalences and course of hormonal changes more precisely and to identify the most appropriate time of endocrine assessment to optimize treatment protocols.

Funding

This work was supported by grants from the National Research, Development and Innovation Office (OTKA K-134555, OTKA FK-146334 to PT), National Clinical Neuroscience Laboratory (RRF-2.3.1-21-2022-00011), the Thematic Excellence Program 2021 Health sub-programme of the Ministry for Innovation and Technology in Hungary, within the framework of the EGA-16 project of the University of Pecs (to PT). Project no. TKP2021-NKTA-47 was implemented with the support provided by the Ministry of Innovation and Technology of Hungary from the National Research, Development and Innovation Fund, financed under the TKP2021-NKTA funding scheme. Funding through the National Cardiovascular Laboratory Program (RRF-2.3.1-21-2022-00003) was provided by the Ministry of Innovation and Technology of Hungary from the National Research, Development and Innovation Fund; Project no. 135784 was implemented with the support provided from the National Research, Development and Innovation Fund of Hungary, financed under the K_20 funding scheme and the European University for Well-Being (EUniWell) program (grant agreement number: 101004093/EUniWell/EAC-A02-2019/EAC-A02-2019-1). The funding sources had no role in the study design; in collection, analysis, and interpretation of data; in writing and submitting this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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