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REVIEW ARTICLE

Hypopituitarism post traumatic brain injury (TBI): review

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Abstract
Post-traumatic hypopituitarism (PTHP) is an important and relatively common complication of TBI (traumatic brain injury). A number of studies have shown that this clinical phenomenon can occur soon after TBI (acute) or later in the chronic phase. Patients with moderate to severe TBI are at a particular risk of developing PTHP. In the acute setting, it is important to monitor patients for hypoadrenalism as this confers a high risk for morbidity and even mortality. The gonadotrophin, growth hormone and TSH deficiencies are better defined in the chronic phase. Untreated PTHP can lead to delayed recovery, impaired rehabilitation and persistent neuropsychiatric symptoms. This review will discuss the frequency and natural history of PTHP and its clinical implications and propose a pathway for investigation and management of this still under-recognised entity.

Keywords Brain · Hypopituitarism · Injury · Post · Traumatic

Introduction

Traumatic brain injury (TBI) is defined as a non-degenerative and non-congenital insult to the brain from an external mechanical force causing temporary or permanent neurological dysfunction, which may result in impairment of cognitive, physical and psychosocial functions [1]. Worldwide, TBI has been estimated to affect 69 million (95% CI 64–74 million) people each year [2]. The overall incidence of TBI per 100,000 in Europe is estimated at 1012 cases (95% CI 911–1113) [2]. There is no exact data on the incidence of TBI in Ireland. However, Headway (Irish brain injury services and support group) estimates that between 9000 and 11,000 people sustain a traumatic brain injury annually in Ireland. Men are twice as likely to suffer head injury compared with women [3].

Hypopituitarism, defined as a deficiency in the production of one or more of the pituitary hormones, has been recently recognised as an important and relatively common complication of TBI [4]. Unrecognised post-traumatic hypopituitarism (PTHP) has been associated with significant acute and long-term morbidity and possibly mortality among patients with moderate and severe TBI. This short review will discuss the frequency and natural history of anterior PTHP and its clinical implications and propose a pathway for investigation and management of this still under-recognised entity.

Prevalence of PTHP

PTHP has been a recognised clinical entity for a century now [5]. Historically, however, it was thought to be a rare condition. This view has changed over the last 15 years as a number of seminal publications have shown PTHP to be a common complication of TBI, especially the moderate and severe forms. Traditionally and in most of the studies, the Glasgow Coma Scale (GCS) has been used to classify the severity of TBI from mild (GCS 13–15), moderate (9–12) and severe (3–8) [6]. Tables 1 and 2 summarise the results of some of the more detailed studies in these fields. A meta-analysis has found the prevalence of PTHP for at least one pituitary hormone deficiency to be as high as 28%, with growth hormone deficiency being the commonest reported deficit [4]. While the overall and specific hormone deficiencies vary considerably between studies (Table 1), they all agree that a significant percentage of survivors of TBI will have some degree of hypopituitarism. The inconsistency in the reported prevalence of PTHP can be explained by varying cohort characteristics, by the timing of testing (see below) and importantly by

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Table 1 Prevalence of pituitary hormonal deficits occurring within 1 month of traumatic brain injury

Study	Number of participants	Severity (GCS)	Median age at TBI (years) (range)	Timing of testing post TBI (days)	Anterior pituitary			
					ACTH (%)	FSH/LH (%)	GH (%)	TSH (%)
Alavi et al. [7]	58	< 14	(16–65)	0–7	10.3	–	–	–
Agha et al. [8]	50	8–13	37 (15–65)	7–20	16	80	18	2
Hannon et al. [9]	100	Moderate–severe	33 (18–75)	1–22	78	–	–	–
Klose et al. [10]	46	3–15	38 (19–63)	0–12	4	67	–	33
Olivecrona et al. [11]	45	≤ 8	-(15–64)	0–1 0–4	54 70	55 58	30 2	5 27
Tanriverdi et al. [12]	52	3–15	35 (17–65)	0–1	10	41	20	6

GCS Glasgow Coma Scale, *TBI* traumatic brain injury, *ACTH* adrenocorticotropic hormone, *FSH* follicle-stimulating hormone, *LH* luteinising hormone, *TSH* thyroid-stimulating hormone

methodological differences in defining hormone deficiencies. Studies that used confirmatory tests have reported a lower frequency of hypopituitarism [14, 21, 22].

While PTHP can occur at all grades of TBI, the prevalence of PTHP appears to be higher among those with severe head injury. In one meta-analysis, the pooled prevalence of hypopituitarism in mild, moderate and severe TBI has been estimated at 16.8%, 10.9% and 35.3%, respectively [4]. However, when more robust criteria had been used to define hypopituitarism, the prevalence of TBI among those with milder forms of TBI attending emergency departments has been shown to be low [23].

The natural history of PTHP

A small number of longitudinal studies have examined the natural history of PTHP from the acute phase to the chronic phase [12, 15, 19]. The data shows that pituitary dysfunction can occur early following trauma and may recover in some patients in the post-acute phase. Conversely, new pituitary hormone abnormalities can become apparent later on. In one study, the authors and their colleagues studied 50 patients with moderate or severe TBI, defined according to the GCS scores, and found a relatively high frequency of early pituitary hormone abnormalities, some of which recovered later while new abnormalities had become apparent at the 6-monthly assessment (Fig. 1) [8]. In particular, gonadotrophin (sex steroids)

Table 2 A sample of studies assessing the prevalence of pituitary hormonal deficits diagnosed in the chronic phase post traumatic brain injury

Study	Number of participants	Severity (GCS)	Median age at TBI (years) (range)	Timing of testing post TBI (months)	Anterior pituitary			
					ACTH (%)	FSH/LH (%)	GH (%)	TSH (%)
Abadi et al. [13]	75	9–13	38 (15–54)	3	13	16	24	5.3
				6	4	10.7	9.3	2.7
Agha et al. [14]	102	3–13	28 (15–65)	6–36	12.7	11.8	10.7	1
Aimaretti et al. [15]	70	3–15	39	3	8.5	17.1	38.5	5.7
				12	7.1	11.4	38.6	5.7
Bondanelli et al. [16]	50	3–15	37.6 (20–87)	12–64	0	14	28	10
Hannon et al. [9]	32	< 14	–	6–24	18.8	3.1	18.8	0
Klose et al. [17]	104	3–15	41 (18–64)	13 (10–27)	5	2	15	2
Kozlowski Moreau et al. [18]	55	3–15	36.1	> 12	27.3	3.6	63.6	21.8
Krahulik et al. [19]	186	3–14	36 (18–65)	12	–	5.6	13.5	–
Schneider et al. [20]	78	3–15	36	12	9	21	10	3
Tanriverdi et al. [12]	52	3–15	35 (17–65)	12	19.2	7.7	37.7	5.8

GCS Glasgow Coma Scale, *TBI* traumatic brain injury, *ACTH* adrenocorticotropic hormone, *FSH* follicle-stimulating hormone, *LH* luteinising hormone, *TSH* thyroid-stimulating hormone

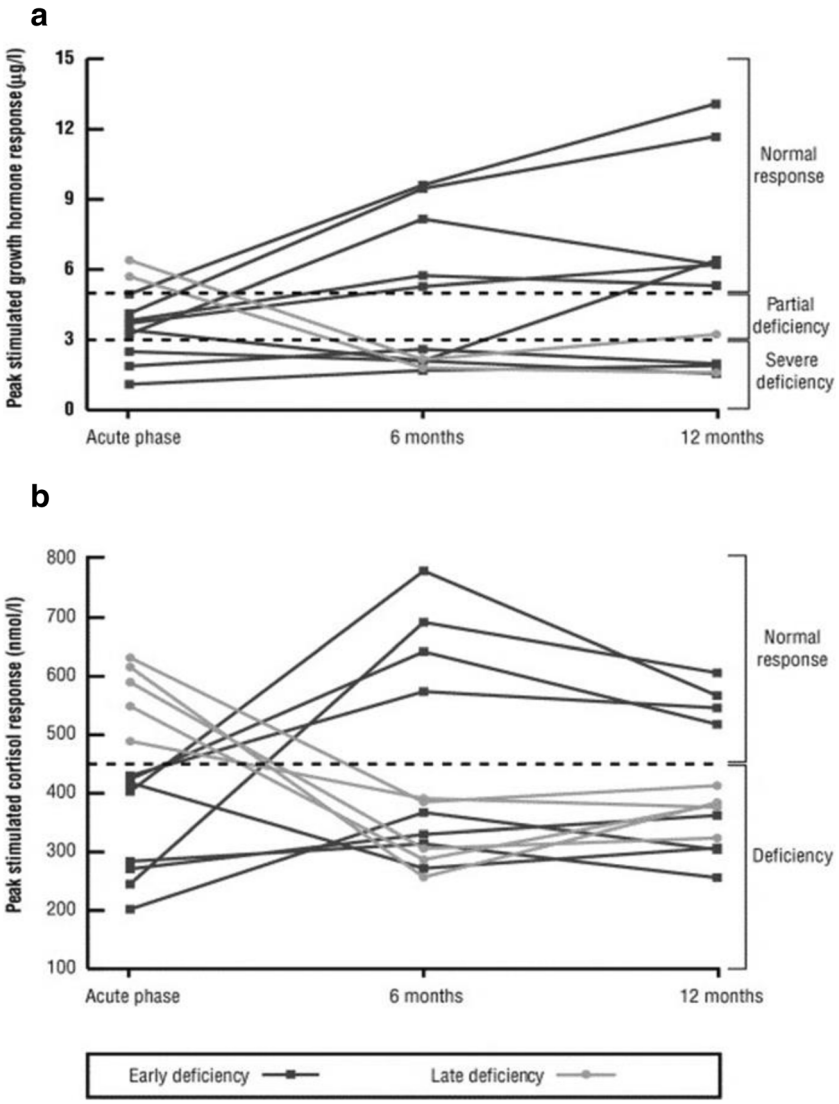

Fig. 1 Peak growth hormone (GH) (A) and cortisol (B) responses to glucagon stimulation in patients with early and late growth hormone and adrenocorticotropin hormone-cortisol deficiencies showing recovery of GH and cortisol secretion in some patients in the post-acute phase while other patients developed new deficiencies later in the chronic phase of TBI [8] (normal responses are GH above 5 mcg/l and cortisol above 450 nmol/l, see body of text for more information)

deficiencies are very common (80%) in the acute phase but are recovered in the majority of patients later [8]. In another study, 50% of patients had developed at least one anterior pituitary hormone deficiency at 12 months with a significant proportion of patients experiencing either a worsening or an improvement of pituitary function [12].

Pathophysiology

The pathophysiology of PTHP is incompletely understood. It is however thought to be multifactorial. Certainly, ischaemic injury to the pituitary gland (+/− hypothalamus) seems to play a major role in the development of PTHP, and this has been supported by post-mortem studies in patients who died shortly after TBI [24–26]. Direct injury to the pituitary gland, infundibulum and/or hypothalamus that may occur at the time of trauma has been implicated [27]. Pressure on the pituitary gland due to haemorrhage into either the sella turcica or the gland itself and hypothalamic nuclei may play a role in the development of PTHP [24–26]. Secondary injury from hypotension and/or hypoxia may be implicated in some cases. Finally, in the acute phase, medications used in the neurosurgical intensive care unit (ICU) setting can occasionally cause hypothalamic-pituitary-adrenal (HPA) axis suppression [28]. Imaging studies suggest vascular /ischaemic injury as contributory to the development of PTHP with magnetic resonance imaging (MRI) showing pituitary gland swelling in the acute phase of the injury [29] and pituitary volume loss or empty sella in the chronic phase [30] (Fig. 2).

Clinical implications of PTHP

The consequences of specific hormone deficits are summarised in Table 3. In the acute phase of TBI, ACTH-

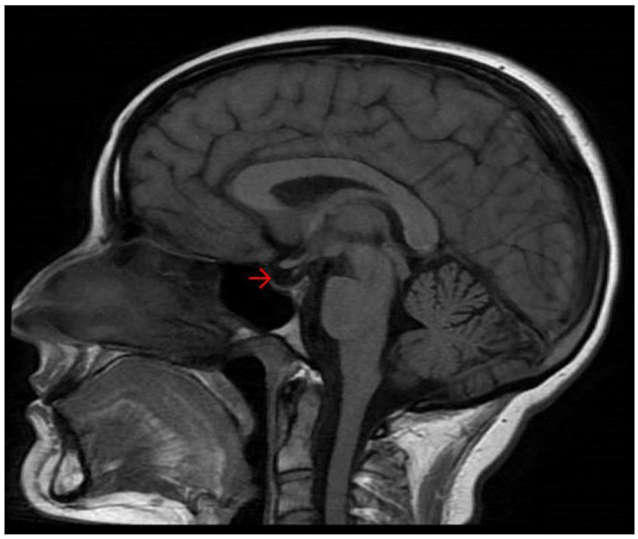

Fig. 2 Pituitary MRI showing empty sella turcica resulting from pituitary infarction following traumatic brain injury (arrow)

cortisol deficiency has been associated with increased morbidity and mortality [9]. One large study showed ACTH/cortisol deficiency in the acute setting to be associated with a significantly higher mortality compared with TBI patients with a normal serum cortisol level [9]. Another study showed that lower cortisol levels were associated with lower blood pressure and higher vasopressor use [28].

In the chronic phase, patients who developed PTHP were shown to have an unfavourable lipid and body composition profiles, as well as worsened health-related quality of life (QoL) scores and neuropsychiatric complications particularly in those with growth hormone (GH) insufficiency [10, 31]. Post-traumatic GH deficiency has been associated with impaired exercise capacity [32]. GH replacement in this group of patients has been shown to improve QoL [33].

Table 3 Signs and symptoms of hypopituitarism

Deficient hormone	Symptoms	Signs
ACTH	Weakness, anorexia, nausea, vomiting, weight loss, arthralgia, abdominal pain	Addisonian crisis especially during acute illness characterised by hypotension, hyponatremia, hypoglycaemia, hypercalcemia, anaemia, eosinophilia
TSH	Dry skin, cold intolerance, dry skin, constipation, hoarseness, neuropsychiatric symptoms	Bradycardia, anaemia, myopathy, hypothermia
LH/FSH	Oligo/amenorrhea (women), decreased libido, erectile dysfunction (men), infertility, sweating, depression	Reduced secondary sexual characteristics, decreased lean body mass, gynecomastia, atrophic testes
GH	Poor QoL, decreased energy, low mood, poor memory, neuropsychiatric symptoms	Decreased muscle mass, increased fat mass, altered metabolic profile, decreased exercise capacity, reduced BMD
Prolactin	Failure of post-partum lactation	
Vasopressin	Polyuria, polydipsia, nocturia, urinary incontinence	Dehydration, hypernatremia

ACTH adrenocorticotropic hormone, *TSH* thyroid-stimulating hormone, *LH* luteinising hormone, *FSH* follicle-stimulating hormone, *GH* growth hormone, *QoL* quality of life, *BMD* body mineral density

Screening

Who to screen

Overall, the relatively high frequency of PTHP was better established in patients with moderate or severe TBI based on the GCS scores, while a low incidence of hypopituitarism was seen in those with milder forms of TBI when robust screening was conducted [34, 35]. Severe TBI seems to confer the highest risk of developing PTHP [34–36]. Other risk factors for the development of PTHP include older age, diffuse axonal injury, basal skull fractures, motor vehicle accident TBI and those with post-traumatic seizures, intracranial haemorrhage, petechial brain haemorrhages and/or focal cortical contusions [36–38]. In patients classified as mild TBI, screening is recommended for those with complicated mild TBI described as need for hospitalisation for more than 24 h and need for ICU monitoring and/or neurosurgical intervention and any anatomical changes on initial brain imaging [39]. Thus, currently, screening is recommended for patients after moderate and severe TBI and for those with complicated mild TBI [39].

When and how to screen (Fig. 3)

Acute phase

In acutely ill patients, it can be difficult to differentiate pathological endocrine deficiencies from adoptive responses to acute illness, and therefore, we do not recommend a full comprehensive pituitary assessment. However, acute phase ACTH/cortisol deficiency is potentially life threatening. In otherwise well patients, a dynamic test such as the insulin tolerance test (ITT) or the synacthen (corticotrophin) test is used to assess the integrity of the HPA axis; but the former is not practical/potentially dangerous and the latter is

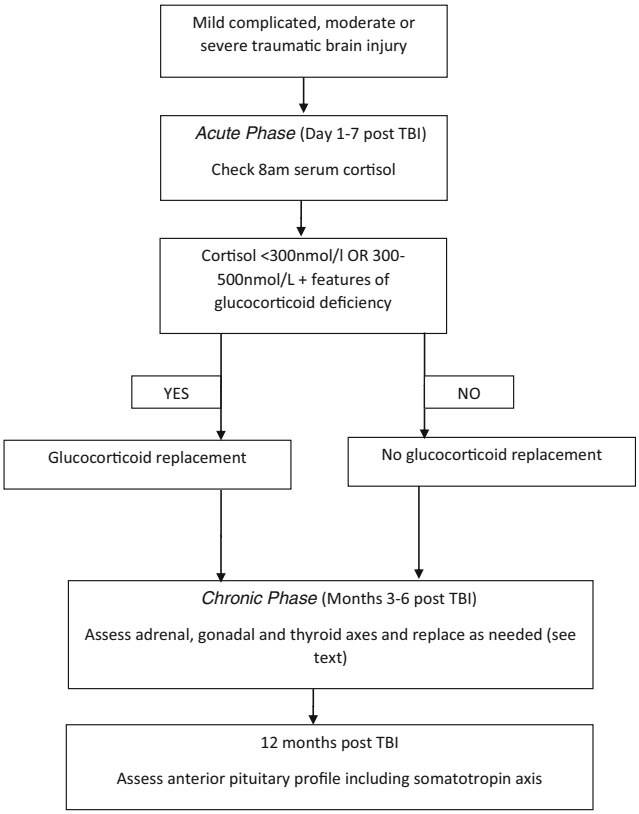

Fig. 3 Algorithm for the screening and management of post-traumatic hypopituitarism

unreliable in the acute setting. Instead, serial morning cortisol measurements should be undertaken as a guide to possible/probable ACTH deficiency. An acute phase cortisol level below 300 nmol/l is suggestive of adrenal insufficiency [40], and treatment with stress doses of glucocorticoids (GCs) should be considered (Fig. 3). Levels of 300–500 nmol/l should be interpreted in the clinical context. Features suggestive of adrenal insufficiency as listed in Table 3 should alert the clinician, and treatment with GC replacement may be warranted.

Chronic phase

In most of the studies, chronic assessment of pituitary function is carried out for 3 months or more post initial injury (Table 2). Basal pituitary hormonal evaluation including thyroid function tests (TFTs), gonadotrophins and sex steroid levels should be carried out. Additionally, adrenal axis function should be formally assessed with the synacthen test or the ITT although we prefer the former due to ease of use. Patients who are deficient should be treated appropriately with a view to repeat testing in a year to assess for possible recovery.

GH deficiency is better assessed at 6 to 12 months (we prefer 12 months) post TBI as early deficiency can recover in many patients in the first few months (Fig. 1), and the assessment is complex requiring a dynamic test such as the ITT or the glucagon stimulation test [41]. GH replacement is indicated for those with severe GH deficiency as defined by GH research society [41]. Figure 3 gives guidance on screening for PTHP in the acute and chronic settings [42].

Conclusion

Post-traumatic hypopituitarism is emerging as a common and significant clinical entity particularly among patients with significant head injury. Clinicians who deal with patients with TBI should be aware of the possibility of PTHP as a cause of delayed recovery, impaired rehabilitation and persistent neuropsychiatric symptoms. In the acute setting, adrenal insufficiency is potentially life threatening and thus needs particular attention. Full assessment of pituitary function is indicated in the chronic phase to detect potentially treatable pituitary deficits which may aid recovery and optimise rehabilitation.

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