Hypopituitarism following Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is a worldwide public health problem and an important cause of hypopituitarism. The incidence of hypopituitarism following moderate to severe TBI varies in different studies and may occur as multiple or isolated hormonal deficiencies, with gonadotrophin and growth hormone insufficiencies predominating, particularly in the acute setting. Adrenocorticotropic hormone deficiency is also common during the recovery phase. Pituitary function assessment in the acute phase post TBI is subject to multiple caveats and pitfalls due to hormonal alterations which occur as normal physiological responses to critical illness and the effects of drugs that are used in the intensive care unit. Nonetheless, assessment of the hypothalamo-pituitary-adrenal axis is of paramount importance during this period. Predictors of hypopituitarism during the acute phase of TBI remain unclear - further research is warranted.

Keywords

Traumatic brain injury, hypopituitarism, pathophysiology, incidence, assessment.

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Introduction

Traumatic brain injury (TBI) is a major public health problem worldwide as it is the principal cause of death and disability among young adults, resulting in physical, emotional, social, cognitive and behavioural impairments, leading to poor quality of life.[1-3] The most common causes of TBI include motor vehicle accidents, violence, sport injuries, falls and child abuse. Children younger than 4-5 years of age, young adults (aged 15-24 years) and the elderly (older than 65 years of age) are the age groups most at risk.[2-3]

Hypopituitarism is becoming an increasingly recognized complication following TBI, ranging from total to isolated deficiencies.[2] It can occur in the acute, post-acute recovery or chronic phase (after 1 year). Prevalence of hypopituitarism varies widely between studies, possibly due to differences in inclusion criteria, dynamic tests employed, timing of testing post TBI and choice (if any) of confirmatory tests following identification of abnormal results.[1] A pooled prevalence of 27.5% was reported in a systematic review evaluating pituitary function 3 months to 7 years post-TBI. Patients suffering from severe TBI had a higher incident rate of hypopituitarism compared with those sustaining mild or moderate injury.[4] Hypopituitarism post TBI is a dynamic process[1,4], in which adrenocorticotropic hormone (ACTH) deficiency can represent a life-threatening pathology, particularly during the acute phase.

Methods

We performed a Medline/Trip database search to identify relevant studies or systematic reviews on this topic. Search terms used were the various combinations of 'traumatic brain injury'/'head injury'/'brain injury'/'trauma'/'injury', 'pituitary'/'hypopituitarism'/'pituitary dysfunction', 'pathophysiology' and 'assessment'. The search was conducted in December 2014. Case reports, case series and non-original research publications were not included. Articles were included regardless of the date of publication.

Pathophysiology

Primary injury may lead to hypothalamo-pituitary dysfunction by direct mechanical damage to the pituitary gland, pituitary stalk and hypothalamus (table 1). The pituitary gland is particularly vulnerable to mechanical

injury/swelling as it lies within the confined space between the sella turcica and diaphragma sella, and is joined to the hypothalamus by a stalk.[5] The hypothalamo-pituitary axis may also suffer from secondary injury through multiple mechanisms (table 1).

Of note, if the stalk is damaged at the point of attachment to the hypothalamus leaving the rest of the stalk and its vessels intact, anterior pituitary infarction does not occur.[3]

Table 1: Mechanisms of hypothalamo-pituitary injury.[2-3, 5, 7, 26]

Type of injury	Mechanism
Primary injury	- Fractures through sella turcica/skull base - Rotational/shearing injuries (including rupture of pituitary stalk) - oedema
Secondary injury	- skull fracture - haemorrhage - oedema/brain swelling - raised intracranial pressure - hypotension - anaemia - hypoxia - inflammatory - vasospasm - thrombosis -reperfusion injury -denervation (supraoptic and paraventricular nuclei, pituitary stalk or axon terminals in the neurohypophysis, leading to diabetes insipidus) - inflammatory mediators (e.g. nitric oxide, cytokines, free radicals, N-methyl-D-aspartate) -autoimmunity (anti-pituitary antibodies)

Following an ischaemic insult, re-perfusion causes excitotoxicity and oxidative stress which, along with the surrounding inflammation, leads to neuronal cell death through necrosis or apoptosis.[6] Acute hormonal deficiencies, particularly growth hormone (GH) (involved with vascular tone and brain repair processes) and insulin-like growth factor-1 (IGF-1) (important for myelination and prevention of oligodendrocyte apoptosis) may adversely affect repair after TBI. Recurrent mild TBI e.g. contact sports, effects of sedative/anaesthetic agents (such as etomidate and propofol) and the stress of critical illness (transiently suppressing the hypothalamo-pituitary axis) are other mechanisms leading to hypothalamo-pituitary dysfunction.[5]

Dysfunction/infarction of the posterior pituitary is less common than that of the anterior pituitary. This is because vascularisation of the posterior pituitary derives from the short/inferior hypophyseal vessels (arising below the diaphragma sella), while the anterior pituitary's blood supply, namely the long hypophyseal vessels (arising from the subarachnoid space and traversing the diaphragma sella) and portal capillaries in the pituitary stalk, are far more susceptible. Moreover, somatotrophs and gonadotrophs, located in the lateral regions of the anterior pituitary (vascularised by the long hypophyseal vessels), are much more susceptible to damage than the medially located corticotrophs and thyrotrophs (vascularised by short hypophyseal vessels).[2,5]

The syndrome of inappropriate anti-diuretic hormone secretion (SIADH) may develop secondary to cytokine (especially interleukin-6) induced stimulation of vasopressin release.[7] Diabetes insipidus (DI) occurs if the posterior pituitary gland becomes denervated secondary to injury to the paraventricular and supraoptic hypothalamic nuclei, pituitary stalk or axon terminals in the neurohypophysis. Additionally, reversible DI may complicate transient inflammatory oedema surrounding the hypothalamus and the neurohypophysis.[3]

Incidence of Hypopituitarism in the acute and recovery phase of moderate to severe TBI

In the acute phase of moderate to severe TBI, Agha

A *et al* reported that 80% of patients suffered from gonadotrophin deficiency, 18% had GH deficiency, 16% glucocorticoid deficiency, 2% thyroid stimulating hormone (TSH) deficiency[8-9], while cranial DI occurred in 26%.[9] DI occurred in 22 out of 102 consecutive patients presenting with TBI.[10] In a study by Tanriverdi *et al*, 56.5% of individuals had at least one axis affected in the acute phase. 36.9% had isolated hormonal dysfunction, 19.6% suffered from combined hormonal deficiencies, while none had panhypopituitarism. These authors reported no significant difference in anterior pituitary hormone levels between individuals with mild, moderate and severe TBI in the acute phase, with the exception of total testosterone, which was much lower among those suffering from severe injury. The most common deficiencies were gonadotrophin deficiency (41.6%) followed by GH deficiency (20.4%).[11]

The reported incidence of hypopituitarism in the recovery phase post moderate to severe TBI varies in different studies, as summarised in table 2. In a study by Bondanelli *et al*, 30.5% had at least one pituitary axis affected and 1.4% suffered from panhypopituitarism.[12] There was no association between incidence of hypopituitarism and severity of TBI in some studies [6,12-13], while an association was noted in others.[10, 14] GH and gonadotrophin deficiencies predominated in some studies [6,12], while ACTH and gonadotrophin deficiencies predominated in others [8,13-14], as outlined in table 2.

The incidence of hypopituitarism in the chronic/recovery phase post TBI was reported as 35.3% following severe TBI and 10.9% following moderate TBI in a systematic review.[4] New onset deficiencies were seen within the first six months (particularly ACTH deficiency), but not subsequently. In most instances, there was a tendency towards amelioration in pituitary function with time[4,8], with the majority of patients showing complete recovery of hyperprolactinaemia and the gonadotrophin axis. Patients with more severe GH and cortisol deficiency during the acute phase were more likely to remain deficient in these two hormones during recovery.[8]

In a prospective study by Kaulfers *et al*, moderate to severe TBI in children was associated with pituitary dysfunction in 15% of affected individuals at 1-5 weeks, 25% at 2-3 months, 75% at 6 months and 29% at 12 months. Pituitary function generally recovered within a year of TBI. Pituitary hormonal impairment persisting thereafter was isolated, with precocious puberty being the most common (14%), followed by central hypothyroidism (9%) and GH deficiency (5%).[15]

Assessment of pituitary function in the acute phase post-TBI

Several caveats and pitfalls must be considered when assessing pituitary function in the acute phase post TBI.

Anaesthetic drugs (such as etomidate, pentobarbital and propofol) can induce adrenal insufficiency. Vasopressors (such as dopamine agonists) can cause hypoprolactinaemia.[5] Anticonvulsants, sedatives (such as midazolam) and narcotic analgesics (such as morphine and fentanyl) can also affect corticosteroid metabolism or suppress the hypothalamic-pituitary-adrenal axis.[16-17] Hepatic enzyme inducing anticonvulsants, such as carbamazepine or oxcarbazepine, can decrease circulating thyroid hormone in 25-50% of patients (TSH remaining stable) as well as increase the production of sex hormone binding globulin (SHBG) and/or increase breakdown of gonadal hormones, leading to low levels of free gonadal steroids.[18]

An increase in the stress hormones (GH, ACTH, cortisol, vasopressin and prolactin) may occur post-TBI.[18] In polytrauma patients, GH may be normal to low due to reduced secretory pulse amplitude.[19] However, peripheral GH resistance can occur in critical illness, leading to high GH and low IGF-1.[7] Moreover, acute illness causes changes in hormone binding proteins. Alterations in serum albumin and a lowering of cortisol binding globulin (CBG) concentration occur in the first week, causing higher circulating levels of free cortisol albeit a low total cortisol which will not reflect free and bioavailable cortisol.[4,18] High cytokine levels increase corticosteroid metabolism (lowering free cortisol levels), decrease corticosteroid receptors and cause peripheral resistance to glucocorticoids, leading to 'relative adrenal insufficiency'.[19] On the other hand, metabolism of circulating hormones may be reduced by damage or decrease in blood flow of organs/tissues responsible for their metabolism, often leading to higher circulating levels. Diurnal rhythms are often disturbed.[20]

Central hypogonadism and hypothyroidism will occur in most patients, which may be indistinguishable from post traumatic central hypothyroidism and hypogonadism.[18] A drop in tri-iodothyronine (T3) (low T3 syndrome) is observed due to decreased peripheral conversion of thyoxine (T4) to T3. T4 and TSH may remain normal or fall acutely especially following severe injuries.[7, 21]

As a result, whether free or total hormone measurements are taken, interpretation of such measurements is unreliable in the acute phase of TBI. Moreover, a standard Synacthen test does not exclude cortisol deficiency, as the adrenal glands have not yet atrophied in the acute phase and will respond to exogenous ACTH, rendering this test dangerously misleading. An insulin tolerance test (ITT) is relatively contraindicated and dangerous in this setting due to a risk of inducing seizures.[18, 20]

Table 2: *Incidence of hypopituitarism in the recovery phase of patients who had suffered from moderate to severe TBI in different studies.*

Study	Time to testing	Hypopituitarism affecting at least one anterior pituitary hormone	Isolated anterior pituitary deficiencies	Multiple anterior pituitary deficiencies	Pituitary hormonal deficiencies					
					GH	FSH/LH	ACTH	TSH	PrL	DI
Dimopoulou et al [14]	Early recovery phase after weaning from mechanical ventilator	53%	35%	18% (two axes affected)	9% (partially impaired on GHRH testing)	24%	24% (post CRH testing)	15%	U/A	U/A
Agha et al [8]	6 months	U/A	U/A	U/A	13%	23%	19%	2%	U/A	U/A
Agha et al [8]	12 months	U/A	U/A	U/A	10%	13%	19%	2%	U/A	U/A
Agha et al [13]	6-36 months (median 17 months)	28.4%	22.5%	5.9%	10.7%	11.8%	12.7%	1%	U/A	U/A
Agha et al [10]	6-36 months (median 17 months)	U/A	U/A	U/A	U/A	U/A	U/A	U/A	U/A	6.9%
Popovic et al [6]	1 year	34%	24%	10%	15%- severe deficiency 15%- insufficient	9%	7%	4%	7%	4.5%
Bondanelli et al [12]	6 months to 1 year	26.4%	19.4%	5.5%	14%	14%	4%	4%	U/A	1.4%*

FSH- Follicle stimulating hormone; LH- Luteinizing hormone; ACTH- adrenocorticotropic hormone; TSH- Thyroid stimulating hormone; PrL-Prolactin; CRH- Corticotropin releasing hormone; GHRH- Growth hormone releasing hormone; U/A-unavailable *isolated

Since the endocrine response in the acute phase post TBI is markedly dynamic, taking regular hormonal measurements is acceptable in a bid to detect evolving endocrine pathology. However, this approach is likely to increase the risk of false positive results, rates of which are influenced by the accuracy of the specific assay employed for diagnostic purposes.[20] Given that adrenal insufficiency is life threatening and dynamic testing is impractical in critically ill patients, daily early morning cortisol should be measured for the first seven days following brain injury.[3,19] One-off measurements are unreliable as acute hypopituitarism may be transient, occur unpredictably in the first seven to ten days after TBI and may be self-resolving.[19] In the absence of any glucocorticoid supplementation, a morning cortisol of less than 200nmol/L, is highly indicative of glucocorticoid insufficiency and the patient should be given intravenous hydrocortisone. If the early morning cortisol level lies between 200 and 500nmol/L, and the patient shows features of adrenal insufficiency a trial of

glucocorticoid replacement should be initiated.[3-4,8] Other reviews recommend treatment when the morning cortisol level is below 300nmol/L.[1,19] Gonadal, thyroid and GH assessment in the acute phase is not essential, as replacing these hormones during critical illness has not been shown to improve outcomes; moreover any changes are likely to be adaptive responses to critical illness.[3,19] Cranial DI can be diagnosed using Seckl and Dunger criteria.[22] Similarly, SIADH is diagnosed using established clinical guidelines.[23]

Assessment of pituitary function in the recovery/chronic phase

Assessment should commence by taking a complete history and examination to assess for hypopituitarism and hyperprolactinaemia. Table 3 demonstrates the various signs and symptoms associated with hypopituitarism. Hyperprolactinaemia may cause galactorrhoea and symptoms of gonadotrophin deficiency. A serum sodium and a blood glucose will

help to exclude hyponatraemia and hypoglycaemia respectively, as seen in ACTH deficiency (hyponatraemia may also be seen in TSH deficiency). Hypernatraemia or a serum sodium towards the upper end of normal may be found in DI. Pituitary function tests should include basal serum 7-9am cortisol (if low, a serum ACTH should be requested), T4, T3 and TSH levels, luteinizing hormone, follicle stimulating hormone, oestradiol and SHBG, prolactin, IGF-1 and paired urine and plasma osmolalities. A basal cortisol of less than 100nmol/L indicates adrenal insufficiency, while more than 400nmol/L indicates adequate function of the hypothamo-pituitary-adrenal axis. If the basal cortisol lies between 100 and 400 nmol/L and/or GH deficiency is suspected, an ITT or glucagon stimulation test is recommended. GH releasing hormone and the arginine/GH releasing peptide provocative test constitute two alternative dynamic tests of GH reserve. Magnetic resonance imaging should be carried out (unless organised earlier) if the above tests indicate the possibility of hypothalamic-pituitary dysfunction.[24-25]

Table 3: *Signs and symptoms associated with the various hormonal deficiencies present in hypopituitarism.*[2, 21, 27]

Hormone deficiency	History	Examination
ACTH	Lethargy, weakness, myalgia, nausea, anorexia, weight loss	Pallor, hypotension
Gonadotrophins	decreased libido, dyspareunia, amenorrhoea/oligomenorrhoea	Fine wrinkles, breast atrophy, paucity of body hair
TSH	Weight gain, cold intolerance, constipation, fatigue, low mood	Dry skin, slow relaxing reflexes, bradycardia
GH	Impaired concentration, memory and cognitive function, low mood, reduced exercise tolerance	Central adiposity, reduced lean mass
Vasopressin	Polyuria and polydipsia especially nocturnal	

Conclusion

The investigation and management of pituitary dysfunction in the acute phase post TBI remains challenging, particularly given the paucity of good quality research data. Well designed studies are needed to identify possible predictors of permanent hypopituitarism /pituitary dysfunction, while guiding the most appropriate timing and dosing of hormonal replacement in an intensive care/acute setting.

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