Review Article

Pituitary and/or hypothalamic dysfunction following moderate to severe traumatic brain injury: Current perspectives

Zeeshan Javed, Unaiza Qamar[1], Thozhukat Sathyapalan

Department of Academic Endocrinology, Diabetes and Metabolism, Hull York Medical School, University of Hull, Hull and East Yorkshire NHS Trust, Hull, UK, [1]The Children's Hospital and Institute of Child Health, Department of Clinical Pathology, Punjab Health Department, Lahore, Pakistan

ABSTRACT

There is an increasing deliberation regarding hypopituitarism following traumatic brain injury (TBI) and recent data have suggested that pituitary dysfunction is very common among survivors of patients having moderate-severe TBI which may evolve or resolve over time. Due to high prevalence of pituitary dysfunction after moderate-severe TBI and its association with increased morbidity and poor recovery and the fact that it can be easily treated with hormone replacement, it has been suggested that early detection and treatment is necessary to prevent long-term neurological consequences. The cause of pituitary dysfunction after TBI is still not well understood, but evidence suggests few possible primary and secondary causes. Results of recent studies focusing on the incidence of hypopituitarism in the acute and chronic phases after TBI are varied in terms of severity and time of occurrence. Although the literature available does not show consistent values and there is difference in study parameters and diagnostic tests used, it is clear that pituitary dysfunction is very common after moderate to severe TBI and patients should be carefully monitored. The exact timing of development cannot be predicted but has suggested regular assessment of pituitary function up to 1 year after TBI. In this narrative review, we aim to explore the current evidence available regarding the incidence of pituitary dysfunction in acute and chronic phase post-TBI and recommendations for screening and follow-up in these patients. We will also focus light over areas in this field worthy of further investigation.

Key words: Follow-up, Future perspectives, incidence, pituitary dysfunction, traumatic brain injury

Introduction

Traumatic brain injury (TBI) has been mentioned as a principal cause of disability and death in young adults.[1,2] The consequences after TBI not only include physical disabilities but also lead to seizure disorders, long-term psychological, behavioral, and cognitive dysfunction.[3,4] It has been suggested that 66–100% permanent neurological disability can develop in subjects after moderate to severe TBI [Table 1 explains severity and phases of TBI][3,5,6] which has made it a major public health problem. Therefore, it has been suggested that prevention is of paramount importance given the high toll of long-term complications.[7]

There is an increasing awareness regarding hypopituitarism following TBI which is defined as a documented biochemical deficiency in at least one endocrine axis which might be caused by either an inability of the gland

Corresponding Author: Dr. Zeeshan Javed, Department of Academic Endocrinology, Diabetes and Metabolism, Hull York Medical School, University of Hull, Hull and East Yorkshire NHS Trust, Hull, UK.
E-mail: Zeeshan.javed@hyms.ac.uk

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Table 1: Severity and phases of TBI[5,6]

Severity	Phases
Mild TBI: GCS OF 13–15 Moderate TBI: GCS OF 9-12 Severe TBI: GCS OF 3–8	Acute phase: Generally accepted as the first 10-14 days after TBI Chronic (postacute) phase: At least 3 months after TBI

TBI: Traumatic brain injury; GCS: Glasgow Coma Scale, GCS is commonly used in routine clinical practice to assess severity of head injury. GCS evaluates verbal and motor responses and eye opening on a scale of 3–15

itself to produce hormones or an insufficient supply of hypothalamic-releasing hormones.[8,9] Recent data have suggested that pituitary dysfunction is very common among survivors of moderate to severe TBI, which may evolve or resolve over time.[10-12] There are some studies that have suggested lower prevalence of hypopituitarism after TBI and explained that the prevalence is affected by use of distinct dynamic tests and cut-off values.[13,14]

Previously, the neurological sequel after TBI was attributed to postconcussion syndrome because of close resemblance to features of pituitary dysfunction which might have been overlooked and could be a reason for long-term morbidity in these patients.[2] Due to high prevalence of pituitary dysfunction and its association with increased morbidity and poor recovery in subjects after moderate to severe TBI and the fact that it can be easily treated with hormone replacement,[9] it has been suggested that early detection and treatment is necessary to prevent long-term neurological consequences.[9,15-18]

In this narrative review, we aim to explore the current evidence available regarding the incidence of pituitary dysfunction in the acute and chronic phase post-TBI and recommendations for screening and follow-up in these patients. We will also focus light over areas in this field worthy of further investigation.

Possible Underlying Pathological Mechanisms

The pituitary gland lies within a bony enclosure called the sella turcica supplied mainly by long hypophyseal vessels. The inferior hypophyseal artery supplies a small part of anterior pituitary gland and entire poterior pituitary gland.[2,19,20] The cause of pituitary dysfunction after TBI is still not well understood, but evidence suggests few possible mechanisms:[21]

- Primary injury
- Secondary injury by events like hypoxia, brain swelling, hypotension, anemia
- Stress of critical illness and possible effects of medications.

The pituitary gland is at risk of damage at time of injury because of its position within the sella turcica. Basal skull fractures and subsequent fracture of sella can directly damage pituitary gland, infundibulum and hypothalamus especially by rotational and shearing impact during injury. Hemorrhage in sella turcica and within gland due to fractures can further damage the glands.[21,22] One recent study found 43% showed acute infarcts of varying size and postulated that direct injury through axonal shearing stress can lead to pituitary and hypothalamic damage.[23]

Secondary insults such as hypotension, hypoxia, increased intracranial pressure, changes in cerebral blood flow, and metabolism often accompany major injury, which may lead to ischemic damage to pituitary gland.[11,17] The blood supply to anterior-pituitary is at increased risk of damage because it is supplied mainly by long hypophyseal vessels and portal capillaries in pituitary stalk and blood supply to posterior gland is less susceptible to damage as it is supplied by short hypophyseal vessels. It is evidenced by fact that anterior-pituitary dysfunction is more common than posterior-pituitary dysfunction in survivors of TBI.[11,24] This concept is further supported by studies using magnetic resonance imaging (MRI) to look at the pathological changes in pituitary gland of patients admitted after TBI and found that in acute phase the pituitary gland is enlarged as compared to healthy control subjects with associated pathologies such as infarction, hemorrhage, signal problems, and pituitary stalk transection.[21,25,26] In another study looking at morphological changes of the sella region in TBI patients using MRI or CT Scan found 80% of patients who later developed hypopituitarism had sella abnormalities with most common findings were reduced pituitary volume or empty sella followed by defects of pituitary perfusion and abnormal pituitary signaling.[27] Other studies found that different patterns of hormonal insufficiency with deficiency have been seen mainly in growth hormone (GH) and gonadotropin levels because somatotropic and gonadotrophic cells are located in lateral parts of pituitary which are more susceptible to ischemic damage after head trauma as these areas are supplied by long hypophyseal vessels that are at increased risk of damage after TBI. The corticotrophs and thyrotrophs are located mainly in the central parts of pituitary gland and, therefore, less susceptible to damage because mainly short hypophyseal vessels supply them.

Few studies have also looked into the impact of acute stress changes and medication on pituitary function and recovery of patients. One of the studies found that almost 50% of the patients had acute secondary adrenal-insufficiency after moderate-severe head injury and suggested that excessive

use of medications (opioids, phenobarbital, high dose heparins, and etomidate) commonly used in Intensive Care Unit is one of the reasons for aggravating clinical picture and can alter efficacy of endocrine testing, therefore special attention should be given to monitoring of cortisol levels to prevent prolonged damage due to hypotension and resulting ischemia.[28-30]

Autoimmunity could also play a role in pituitary dysfunction after TBI. It has been investigated and shown in few studies that pituitary dysfunction was more severe in those patients who were positive for anti-pituitary antibodies (APA) and anti-hypothalamic antibodies (AHA).[31,32] Recently, a 5-year prospective study has also shown that pituitary dysfunction was remarkably higher in patients with positive AHA and APA antibodies.[33]

Genetic predisposition has also been postulated as one of underlying mechanisms for pituitary dysfunction after TBI.[34,35] Apolipoprotein E (ApoE) is a vital protein required for cell membrane repair, which also spreads neuritis following injury. ApoE genetic polymorphism has been studied in TBI patients that revealed poor outcome if they were positive for ApoE4 but better outcome has been seen in patients who had ApoE3 genotype.[36-39]

Incidence of Pituitary Dysfunction in Acute Phase Following Traumatic Brain Injury

Current evidence suggests that results of recent studies focusing on incidence of hypopituitarism after TBI[2,15,40] are varied and possible reasons could be difference in patient selection, severity of injury, methods used, study design and timing of assessment.

Few studies showed that serum cortisol increase in acute-phase and then back to normal after several days.[41,42] Cernak *et al*., found low cortisol on days 1–3 but rose to high levels 5–7 days after injury. Another study[43] found high cortisol level indicated abnormal activation of hypothalamic-pituitary-adrenal (HPA)-axis that failed to suppress by high dose dexamethasone administration. Recent studies also found adrenal insufficiency in acute postinjury phase but degree of insufficiency was not consistent as one study[44] found 16%, other[28] found 53% and third one found[45] 9.8%.

The data related to GH in acute phase of TBI are inconsistent and have shown both low[3,46,47] and high basal levels of GH.[48] Few studies have demonstrated reduced GH pulsatile release and blunted response to arginine stimulation 24–48 h after severe TBI, which was associated with poor outcome.[42,49,50] Other studies revealed progressive increase in GH response after 48 h of initial poor response and paradoxical rise in GH levels after intravenous glucose administration in patients with severe injury.[50,51] In contrast, Bondanelli *et al*. studied GH/insulin-like growth factor-1 (IGF-1) axis using basal and dynamic tests in patients during acute phase after severe TBI and found no significant difference in GH secretion as compared to healthy controls, indicating normal GH axis in acute phase of TBI.[52] Only one patient had subnormal response to GHRH plus arginine stimulation. Recently, severe growth hormone deficiency (GHD) has been demonstrated in 18% of patients during acute phase using basal plus glucagon stimulation test and in 20.4% patients using basal GH levels within 24 h of TBI.[44,45]

Similarly, many studies found low testosterone in acute-phase indicating suppression of hypothalamic-pituitary-gonadal (HPG) axis that has been related to severity of head injury.[44,53,54] Another study found suppressed gonadal axis in 32% of subjects and suggested it an adaptive response of body in such patients to decrease use of energy and metabolic substrates by less vital organs.[16]

Evidence related to thyroid and prolactin levels in acute phase are also very inconsistent with some studies have shown elevated levels[41,44,45] while others have found reduced levels[42,44,45] and few have shown no change in their levels.[50]

In summary, some of the acute changes in pituitary function after TBI, such as hypogonadism and hyperprolactinemia reflect adaptive response of body in such situation.[55] However, adrenal insufficiency has been associated with serious consequences which need particular attention to reduce long-term morbidity and improve recovery.[40,56-58]

Incidence of Pituitary Dysfunction during Recovery Phase following Traumatic Brain Injury

The evidence related to the prevalence of pituitary dysfunction in recovery phase is also varied. One of the studies on 22 patients assessed pituitary functions 26 months postinjury and showed 18% had impaired GH response, one patient had impaired cortisol response, one female patient had gonadotropin deficiency, and one had thyroid-stimulating hormone (TSH) deficiency. Some degree of hypopituitarism occurred in 40% of patients with GHD being most common.[59]

Another study[60] enrolled 70 patients and assessed pituitary function 49 ± 8 months after TBI. Results revealed GHD in 14.6%. Free-T4 and TSH were low in 21.7% with impaired cortisol response in 7.1%. Hyperprolactinemia and hypogonadism were rare.

In 2004, another study[53] assessed patients 19 months after TBI using two stimulation tests, revealed 28% had at least one pituitary hormone deficiency with 11% GHD, 12% gonadotropin deficiency, 1% TSH deficiency, 13% hyperprolactinemia, and 1% had panhypopituitarism.

Similarly, many other studies[61-71] revealed figures close enough to above-mentioned studies [Table 2]. However, one recent study[72] selected 170 patients a year after severe TBI and found 24.7% had any form of pituitary deficiency with gonadotropin deficiency was most prevalent. GH, TSH and ACTH deficiency was near to 6%. Several studies have also reported sports-related TBI induced pituitary dysfunction especially those including collision and/or contact as well as high-velocity sports such as soccer, boxing, rugby, football, ice hockey, martial arts, roller skating, motor racing, cycling, skiing, and equestrian sports.[11,73,74] The degree of dysfunction was more if the duration of sports engagement was prolonged and in those who had more head injury episodes. GHD was most common in these patients.[75-79] Few other studies[40] showed that diabetes insipidus was present in 7% patients after head injury and SIADH in around 2.3–36% post-TBI that was mainly transient. Recently, Klose *et al*. assessed the prevalence of GHD 2.5 years after TBI in 439 patients and 124 healthy controls using insulin tolerance test (ITT), pyridostigmine (PD)-GHRH or GHRH-arginine test, local versus guideline cut-off values, single versus repetitive testing, and using different GH assays.[80] They found that the prevalence of GHD was less using local than by guideline cut-off values (12% vs. 19% [PD-GHRH/GHRH-arginine]; 4.5% vs. 5% [ITT, $P = 0.9$]), and by ITT than by PD-GHRH/GHRH-arginine ($P = 0.006$ [local cut-offs]; $P < 0.001$ [guideline cut-offs]). Only 1% had GHD according to 2 tests and GH assessment by the Immulite or iSYS assay caused no significant diagnostic differences. They also observed significant number of false positive results in the control group. However, this study had few limitations; most importantly, the majority of patients involved in this study had mild TBI, second PD-GHRH stimulation is not a well-standardized test and is not used commonly for the diagnosis of GHD[81] and is not pertinent to confirm results acquired from ITT which is more sensitive. Third, GHRH-arginine test was used only for those patients who had contraindications to other tests though it has been more commonly used test and is also more widely available.[81] Recently, a systematic review has been published in which authors compared either the prevalence of abnormal endocrine tests was higher in TBI patients as compared to controls or not and included only those studies that applied at least one endocrine test in a matched control group.[5] They found that pooled prevalence of GHD was 7.7% and 1.4% in patients and controls respectively ($P < 0.001$) according to the results obtained from ITT using local cut-offs values by Klose *et al*.[80] and standard cut-offs used by other studies. The pooled prevalence of GHD according to the combined tests was 11.1% and 1.3% in patients and controls respectively ($P < 0.001$).[5]

Table 2: Prevalence of pituitary dysfunction in postacute phase of TBI[13,18,47,55,62,63,66-74,82-84]

Study	Number of patients	Time to testing (months)	LH/FSH %	ACTH %	TSH %	GH %	Multiple deficiencies %	Hypopituitarism %
Lieberman *et al*., 2001	70	Median 3	1.4	45.7	21.7	14.6	17.1	68.5
Bondanelli *et al*., 2004	50	12-64	14	0	10	8	12	54
Popovic *et al*., 2004	67	12	9	7.5	4.5	15	10	34
Agha *et al*., 2004	102	Median 17	11.8	22.5	1.0	17.6	5.9	28.4
Agha *et al*., 2005	50	6-12	12.5	18.8	2.1	10.4	NR	NR
Aimaretti *et al*., 2005	70	3-12	11.4	5.7	7.1	20	10	22.9
Leal-Cerro *et al*., 2005	170	>12	17.1	6.5	5.9	5.9	8.8	24.7
Herrmann *et al*., 2006	76	Median 20	17.1	2.6	2.6	7.9	6.6	23.7
Schneider *et al*., 2006	78	3-12	20	9	3	10	4.3	36
Tanriverdi *et al*., 2006	52	12	7.7	19.2	5.8	37.7	9.7	50.9
Klose *et al*., 2007	104	Median 13	2	5	2	15	5.8	15
Bushnik *et al*., 2007	64	12	10.9	61	18.8	35.9	NR	90
Bavisetty *et al*., 2008	70	6-9	10.5	0	0	16	7.1	21
Kleindienst *et al*., 2009	23	>24	0	47.8	0	39.1	NR	NR
Srinivasan *et al*., 2009	18	5-12	0	50	22.2	22.2	27.8	55.6
Van der Eerden *et al*., 2010	107	3-30	6.5	5.6	1	1	0	14
Berg *et al*., 2010	246	9-18	9	1	12	5	2	21
Kokshoorn *et al*., 2011	112	Mean 48	0.9	1.8	0	2.7	0	5.4

LH: Luteinizing hormone; FSH: Follicle-stimulating hormone; GH: Growth hormone; ACTH: Adrenocorticotrophic hormone; TSH: Thyroid-stimulating hormone; NR: Not reported

Although the literature available does not show consistent values and there are differences in study parameters and diagnostic tests used, it is clear that pituitary dysfunction is very common after moderate to severe TBI[85-94] and patients should be carefully monitored in order to reduce long-term morbidity and mortality.[15,95-101]

Recommended investigations of assessing pituitary function in acute phase following traumatic brain injury: Caveats and pitfalls

Current evidence suggests that patients having moderate-severe TBI should be assessed for anterior and posterior-pituitary dysfunction in acute phase after TBI (generally first 10–14 days after TBI, Table 1) to diagnose and prevent life-threatening endocrine complications.[102] Those who are at increased risk of developing short and long term endocrine complications, must undergo serial pituitary-function assessments, but it is important to exclude those patients who are not going to get any benefit from hormone replacement therapy such as patients with severe disability or in vegetative state.[53,103]

It is not pertinent and practical to perform dynamic tests in acute phase after TBI, and there is no international consensus on diagnostic cut-off values. Current data related to assessment of pituitary dysfunction in the acute phase demonstrate that changes in levels of GH, Follicle-stimulating hormone/luteinizing hormone (FSH/LH) and TSH are transient and usually recover within 3–12 months after TBI.[5,45,82,83,104,105] Furthermore, the evidence regarding the beneficial effects of FSH/LH, GH, and TSH replacement during acute phase in TBI patients is also not transparent and suggests no benefits.[5,12,106] However, in the acute phase after TBI, it is very important not to miss acute hypoadrenalism, because it can be life-threatening.[28,56,107] It has been recommended, that during acute phase, the prime focus should be adrenal insufficiency that has been shown to be associated with severe hyponatremia, hypoglycemia, excessive need for vasoactive drugs, refractory hypotension, hemodynamic instability, and poor neurological outcome.[28,41,44,56] As the dynamic tests to assess cortisol deficiency are not practical under such situations, the authors recommend basal cortisol <200 nmol/l (7.25 μg/dl) in the acute-stage suggestive of ACTH-deficiency and treatment with glucocorticoids is recommended until after acute-stage when full assessment can be performed.[2,108] If basal cortisol is between 200 and 400 nmol/l (7.25–14.5 μg/dl), treatment should only be commenced if the patient is having signs of adrenal-insufficiency. It is important to remember that cortisol levels can be affected by many factors under this clinical setting such as medications, sepsis and low cortisol-binding-globulin which should also be considered while measuring cortisol levels.

It has also been recommended that rapid diagnosis and treatment of diabetes-insipidus in acute-phase of TBI is required as it is associated with increased mortality due to associated hypernatremia. Although hyponatremia due to SIADH is transient in acute-phase, it should still be looked for, as if undiagnosed can lead to profound hyponatremia that could be fatal.[11]

Recommendations regarding follow-up for pituitary dysfunction in postacute phase following traumatic brain injury

Current evidence shows that there is high risk of hypopituitarism after TBI.[109-113] The exact timing of development cannot be predicted but has suggested regular assessment of pituitary function at least up to 1 year after TBI.[2,114-120] Several prospective studies have looked into the development of pituitary dysfunction 3 and 12 months after TBI[16,45,83,84,104,105] and found that, although pituitary dysfunction develops in the postacute phase that may normalize over a period of 12 months, but new onset pituitary abnormalities may also develop after postacute phase of TBI. The pituitary dysfunction at the end of 12 months varied from 13% to 50%[5] and the most common pituitary-axis affected was somatotropic (GH-axis).

As it is difficult to predict the exact timing of pituitary dysfunction development, current evidence suggests a plan for follow-up of patients after TBI as shown in Figure 1. However, signs and symptoms can be misleading in these patients, it has been suggested that universal screening is

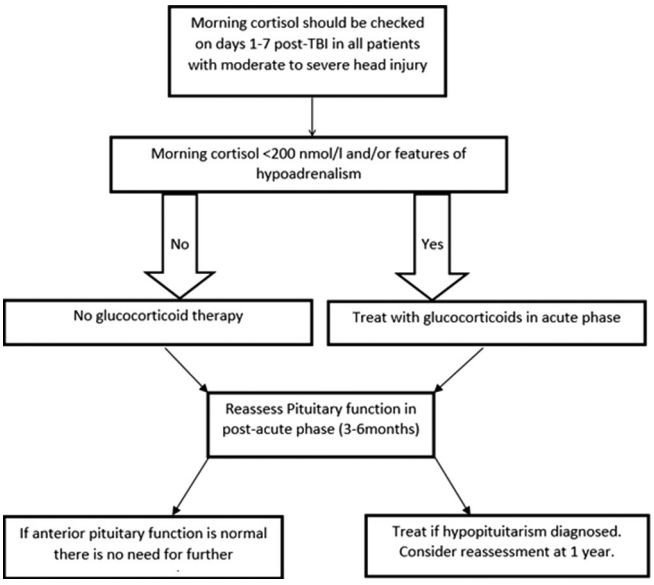

Figure 1: Suggested algorithm for the assessment of patients after traumatic brain injury[5,83]

performed. This would include baseline hormonal work-up and dynamic tests if indicated.[103,121]

Diagnostic tests for evaluating traumatic brain injury induced pituitary dysfunction

Hypothalamic-pituitary-gonadal axis

Gonadotropin secretion in premenopausal women who have had a TBI is assessed by checking oestradiol levels on two or more occasions. In females with central hypogonadism low oestradiol levels will be associated with the absence of elevated FSH. The GnRH-test used to diagnose central hypogonadism lacks both sensitivity and specificity and rarely adds helpful information to basal endocrine levels.[3,5,9] It is recommended that basal levels of oestradiol and gonadotropins associated with appropriate clinical context are sufficient to make diagnosis of central hypogonadism. However, GnRH test can be helpful in cases where patients have normal sex steroid levels but reduced LH/FSH response indicating the patients may be at risk of hypogonadism in future and need regular follow-up. In men, central hypogonadism can best be diagnosed by repeated low levels of morning serum testosterone associated with low/normal LH.[5,9,100]

Also, before confirming diagnosis of central hypogonadism, it is important to exclude hyperprolactinemia as it has been seen to be associated with hypogonadism in some cases that might be due to lesions of pituitary stalk or hypothalamus or drug interference.[5,100]

Somatotroph (growth hormone-insulin-like growth factor-1) axis

It has been recommended, if required, to confirm GHD by a dynamic test unless patients have other pituitary hormone deficiencies associated with low levels of IGF-1[9,122] as the chances of GHD increase in TBI patients if there are additional pituitary axis deficiencies. Although none of the dynamic tests are completely reliable in diagnosing GHD, GHRH + arginine and ITT have been recommended in current literature as tests of choice having similar accuracy in evaluating TBI induced GHD.[5] The recommended cut-off values for diagnosing GHD in GHRH + arginine test and ITT are 9 μg/dl and 3 μg/dl, respectively in case of lean adults[9,122-124] while for children are 20 μg/dl and 8–10 μg/dl, respectively because GH secretory capacity in children is high.[125] Additionally, for patients in transition phase between early adulthood and puberty, cut-off values of 5 μg/dl and 6.1 μg/dl have been suggested in case if ITT is used.[126,127] However, use of these cut-off values in obese and overweight patients can lead to high false positive results because GH secretory response to dynamic tests decreases with increasing BMI in adults that need special consideration when making diagnosis in this particular population.[128-131]

Another test that has been substantially studied and validated in TBI patients is GHRH + GHRP6 (GH-releasing peptide-6) test. It also holds significant accuracy in defining patients with severe GHD and has BMI-dependent cut-off values of 15 μg/dl and 5 μg/dl for lean and obese patients, respectively.[131,132]

Finally, glucagon stimulation test (GST) is also recommended as a good alternative if ITT or GHRH + arginine tests are unavailable or contraindicated. GST has also been suggested to possess a sensitivity and specificity of 100% if a cut-off value of 3 μg/dl is used. However, it is time-consuming and also age and BMI-dependent like other stimulation tests.[122,133]

Hypothalamic-pituitary-adrenal axis

In order to assess HPA axis, morning serum cortisol levels are checked on 2 or more occasions. Levels below <3 μg/dl (83–100 nmol/l) are considered diagnostic and levels >18 μg/dl (500 nmol/l) are considered normal and excludes adrenal insufficiency.[3,5,9,134] Levels between 3 and 18 μg/dl require stimulation test. Various dynamic tests can be used to assess HPA axis including ITT, corticotrophin-releasing hormone test and ACTH test (using either 250 μg or 1 μg (low dose) of corticotrophin).

Some authors have recommended confirming diagnosis only if patients fail two provocative tests.[53] Current evidence suggests that definition of normal or impaired corticotrophin secretion in head injury patients is still under debate, and it is very important to assess the whole scenario of each patient in borderline cases.[5]

Thyrotropin releasing hormone-thyroid stimulating hormone-thyroid axis

The diagnosis of central hypothyroidism in TBI patients is easily made when low serum free T4 is associated with normal or low serum TSH values.[11] Although some studies have used TRH stimulation test to diagnose TSH deficiency in patients having TBI,[59] current evidence suggests serial measurements of free T4 and TSH only as dynamic testing does not add to diagnostic reliability.[135-137]

Evidence related to beneficial effects of treatment after traumatic brain injury

Acute phase

To date, there is no comprehensible evidence that the replacement of FSH/LH, TSH and GH during the acute phase post-TBI is beneficial.[106] Studies have shown that TSH deficiency generally recuperates during or after acute phase and thyroid hormone replacement in critically ill patients has not shown any improvement.[110,138] Similarly,

changes in gonadotropins in the acute phase after TBI are transient and reflect an adaptive response.[45]

Studies related to GH therapy in the acute phase after TBI are conflicting as one prospective, placebo-controlled study[139] showed significant improvements in nutritional and metabolic markers after IGF-1 and GH (0.05 mg/kg/day) therapy while another study revealed increased mortality in critically ill patients.[140] Experimental studies, on the other hand, have shown that GH and IGF-1 play a vital role in neuronal recovery mechanisms after TBI.[141-144] It has been proposed that further placebo-controlled human studies are required to resolve this conflict and currently GH therapy has not been suggested in acute phase after TBI. However, during acute phase, diagnosis and treatment of cortisol deficiency should be done promptly as it can be life threatening.[12,56,107]

Chronic phase

Currently, no studies have been published, assessing the long-term effects of FSH/LH, TSH, and ACTH treatment in TBI patients having pituitary dysfunction.

Recent studies have clearly indicated significant morbidity in TBI patients having GHD including impaired metabolic parameters, increased cardiovascular risk, impaired quality of life (QOL) and cognitive functions, decreased muscle force and aerobic capacity.[5,76,79] To date, few clinical studies and case reports have been published assessing the effects of GH replacement therapy in TBI patients. The results demonstrated significant improvements with GH therapy in patients with moderate to severe TBI in terms of improvement in QOL, cognition, memory, information processing speed, vocabulary, executive functioning, and verbal learning.[145-150] Furthermore, the data also suggest that deficits due to GHD in TBI patients are amenable to treatment and GH therapy seems to be as beneficial as in those patients having GHD due to other causes.[5]

Conclusion

Current evidence suggests high prevalence of pituitary dysfunction after moderate to severe TBI, though the values are varied. The exact timing of occurrence cannot be predicted and a follow-up of at least 1 year with regular pituitary assessment has been suggested regardless of clinical evidence for pituitary dysfunction.

Future Research Perspectives

All previous studies show varied results in postacute phase and can be attributed to lack of one specific dynamic test. Because of this lack of uniformity, it is difficult to select which dynamic test is preferable to assess pituitary function in postacute phase, as pituitary response is very unpredictable after TBI. Hence, further longitudinal studies are required to compare different stimulation tests to standardize the diagnostic strategy. Second, levels of pituitary hormones fluctuate in postacute phase and cannot be correlated with normal ranges. Future directions in this field should be an emphasis in determining approximate levels of hormones at various points in postacute phase to determine the critical values to guide early and timely treatment. Some other areas in this field worthy of further investigation include: What is the normal neurohormonal response to head injury? Are there any gender and age disparities? How to predict TBI induced hypopituitarism and who should be screened? Is it possible to predict recovery of pituitary function? What is the link between hypopituitarism and mortality post-TBI? Does the treatment of chronic hypopituitarism improve the eventual outcome from TBI?

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Conflicts of interest

There are no conflicts of interest.

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