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ORIGINAL ARTICLE

Traumatic Injury to the Brain and Endocrine Evaluation of the Anterior Pituitary a Year After the Event (The TRIBE Study)

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Recent clinical studies have shown that moderate and severe traumatic brain injury (TBI) is a common cause of hypopituitarism. Mild TBI has also been associated with hypopituitarism, which since it is often not evaluated, the hypopituitarism may remain under diagnosed. In this study we aimed at determining the clinical and hormonal profile of mild TBI patients admitted a year after their injury.

Materials & Methods: The sample was a descriptive, prospective cohort in a tertiary hospital. A hypopituitarism clinical evaluation form was used to evaluate the patients for signs and symptoms of hypopituitarism a year after mild TBI. Pituitary hormonal function was tested a year after their injury for IGF-1, FT4, TSH, cortisol, LH, FSH and testosterone.

Results: Six male patients with mild TBI were studied. Mean age was 27 ± 8 years old. All of them had intra-cranial hemorrhage on CT-scan and five underwent emergency decompressive cranial surgery. Evaluation was done 481 ± 67 days after the event. Signs of hypopituitarism were not observed but symptoms of decreased vigor and weight gain was present in five of the six patients. IGF-1 was low in 33% (2/6) and testosterone level was low in 17% (1/6).8 am cortisol levels were equivocal in 83% (5/6) but ACTH-stimulated cortisol values were normal. Thyroid function test were normal for all subjects.

Conclusion: The most common symptoms were weight gain & decreased vigor. Signs of hypopituitarism were not noted among the mild TBI patients. Pituitary hormone testing revealed abnormalities in the somatotrophic & gonadotrophic axes.

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Introduction

Traumatic brain injury is defined as a non degenerative, 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 psychological functions.[1] Severity was assessed on the basis of the Glasgow coma scale at the time of presentation, mild with a GCS of 14-15, moderate for a GCS of 9-13, and severe for GCS of <8.[2]

The Centers of Disease Control and Prevention (CDC) reported in 2006 that in the US, 1.4 million Americans sustained some form of traumatic brain injury (TBI); most of them were treated and released from an

emergency department.[3] The risk of TBI-related hypopituitarism has been reported in a number of clinical studies which indicate that hypopituitarism remain underdiagnosed and its incidence is much higher than expected.[4] In the 2007 Endocrine Society Annual meeting, Kelly presented a summary of prospective cohort studies of chronic post-traumatic pituitary failure for 2000-2006 revealing a 40% incidence of pituitary hormone deficiency, particularly growth hormone deficiency (19%) and gonadal deficiency (15%).[5]

The question "Should every patient with traumatic brain injury be referred to an endocrinologist?" was raised by Aimaretti and Ghigo in 2007.[4] Numerous studies supporting the occurrence of some form of hypopituitarism affirms the need for endocrine work-up post head trauma. The timing of the testing remains a controversy, with studies between the acute phase to 1 year after the event, showing a number of hormonal deficiencies.[6]

Majority of studies available are retrospective, showing 1 or more anterior pituitary hormone deficiency. Among mild traumatic brain injury patients, initial anterior pituitary hormone deficiencies may resolve and new onset hormone deficiencies may be noted on follow up.[7]

This study intends to describe the clinical and biochemical endocrine profile of patients at least one year after sustaining a mild traumatic brain injury.

Materials and methods

This is a descriptive prospective cohort study approved by the University of Santo Tomas Hospital Institutional Review Board. Records all patients admitted for traumatic brain injury between January 1, 2007 and December 31, 2007 were reviewed. A total of 86 patients were admitted during this period.

Inclusion criteria were male or female, age between 18 – 45 years, a history of mild traumatic brain injury at presentation a year prior to January 1, 2008, admitted at the clinical or pay division of the University of Santo Tomas Hospital, discharged alive, able to understand the purpose of the study and obtaining of informed consent. Patients with preexisting pituitary and psychiatric disease, those on any hormone replacement therapy, pregnant women, comatose, or those that could not be contacted were excluded.

Contact numbers were obtained from the charts of the included patients. They were invited to participate in the study, and scheduled to visit the St. Thomas Diabetes Center where informed consent was obtained and clinical and biochemical evaluation was done. A detailed clinical history and physical examination were performed. Clinical manifestations of hypopituitarism were determined using a customized checklist containing several items suggestive of hypopituitarism.

Standard biochemical hormonal tests were done to determine the presence of anterior pituitary hormonal deficiency. All assessments were done at least a year after the traumatic brain injury. Testing started 0800-0900 h after an overnight fast. Undiluted blood samples were drawn from a heparinized cannula inserted in an antecubital vein; insulin growth factor-1, thyroid stimulating hormone, free thyroxine, 8 a. m. serum cortisol with stimulated cortisol levels if needed, follicle stimulating hormone and serum testosterone or serum estradiol were assessed.

Insulin growth factor-1 (IGF-1) levels were used to determine the presence of growth hormone deficiency. A serum IGF-1 concentration lower than the age-specific lower limit of normal in a patient with organic pituitary disease confirmed the diagnosis of growth hormone deficiency.[8] IGF-1 was determined using IMMULITE radioimmunoassay kit with an analytical sensitivity of 20 ng/mL. The normal reference range values are age and sex matched.

Normal range for FT4 was 0.8 to 1.9 ng/dL and for TSH was 0.4 to 4 μIU/mL. Secondary hypothyroidism was defined by low serum FT4 level without appropriate elevation in serum TSH.[9] The IMMULITE

radioimmunoassay kit has an analytical sensitivity 0.3 ng/dL for free T4 and an analytical sensitivity of 0.004 μIU/mL for TSH.

ACTH deficiency was defined by basal cortisol < 7 μg/dL, while cortisol levels > 18 ug/dL were normal. Hypothalamic-Pituitary-Adrenal Axis integrity was confirmed in patients with basal cortisol between 7-18 μg/dL with short ACTH (Synacthen) testing of 250 ug IM. Stimulated cortisol levels determined after 60 minutesr > 20Ug/dL were considered adequate.[7] Electrochemiluminescence immunoassay (ECLIA) kit was used which has a sensitivity of 0.018 μg/dL.

In males, the normal range for LH and FSH are 1.57-8.71 mIU/mL and 0.7-11.1 mIU/mL respectively, and for testosterone is between 280-800 ng/dL. The Electrochemiluminescence immunoassay (ECLIA) kit was used with an analytical sensitivity of 0.069 nmol/L. Estradiol normal values also depend on the phase of the female menstrual cycle. Immulite chemiluminescent immunometric assay was used to determine FSH values with an analytical sensitivity of 0.1 miu/mL.

Male secondary hypogonadism was defined by low testosterone with inappropriately low gonadotropin level and for premenopausal women, amenorrhea in the presence of low serum estradiol without a rise in gonadotropin level.[9]

Results

A total of 86 traumatic brain injury patients, age range 4-84 years, were admitted between January 1st and December 31st, 2007. Of 86 patients, 68 (79%) were males and 18 (21%) were females. Of the total population, 16 patients belong to the pediatric group, and the rest of the subjects were adults. Seventy-two percent (62/86 patients) of the population sustained a mild traumatic brain injury, 8% (7/86 patients) had moderate TBI and 20% (17/86 patients) had severe TBI. Among the mild TBI patients, 52 % underwent a neurosurgical procedure, while the other half was managed conservatively. Most of the moderate (86%) and severe (82%) TBI patients had either craniectomy or craniotomy.

Vehicular accidents were the main cause of traumatic brain injury, composing 66% (57/82) of the population. This was followed by falls 23% (20/82) and fight related injury at 11% (9/82). There were 4 mortalities, three of whom were severe and one moderate TBI, the rest of the patients were discharged following improvement.

Six patients were studied with mild traumatic brain injury. All subjects were male with a mean age of 27 years (SD= 8), height 168 cm (SD= 6.75), weight 67.33 Kg (SD= 5.12) and BMI 24 (SD= 2). Majority of the patients had traumatic brain injury related to motor vehicular accidents. Only one had a fall while attempting to climb a truck while intoxicated. They were all classified as mild traumatic brain injury with a presenting Glasgow coma score of 15 (Table 1).

All of the patients were noted to have intracranial hemorrhage as manifested by CT-scan findings of epidural or subdural hematoma. One patient had multiple facial bone fractures and subsequently underwent reconstructive surgery. Two underwent emergency craniectomy and another two had emergency craniotomy. One patient was managed conservatively. None of them were referred for endocrine evaluation. All of the patients were discharged, following improvement.

The mean duration from the time of injury to the time of the study was 481 days with an SD of 67 days. Follow up durations ranged between 382-590 days. Patients were called into the hospital for clinical evaluation. Systolic blood pressure ranged between 100-130 mmHg while diastolic blood pressure ranged between 70-80 mmHg. Average heart rate was 71 beats per minute. All patients were overweight.

Table 1: Clinical and radiologic profile of mild traumatic brain injury patients

Patient	Age /Sex	Height (cm)	Weight (Kg)	BMI (Kg/m^2)	Nature of TBI	Severity of TBI	CT-scan findings
ED	25	158	60	24	Fall	Mild*	Left temporal epidural hematoma
CM	43	180	75	23	VA	Mild	Right parietal subdural hematoma
RA	23	170	71	25	VA	Mild	Right parieto-occipital Epidural hematoma with a non depressed fracture
JV	28	167	62.9	23	VA	Mild	Falcine hematoma
RC	24	163	65.1	24	VA	Mild	Right parieto-occipital subdural hematoma
JD	21	168	69.9	25	VA	Mild	Left temporal epidural hematoma with multiple facial bone fractures

* Glasgow Coma Score in all patients was 15.

A. Growth hormone deficiency.

None of the patients exhibited visceral obesity. However, five of the six patients (83%) expressed decreased vigor, while two patients (33%) reported social isolation and another two (33%) observed decrease exercise capacity. Two patients did not have any signs and symptoms of growth hormone deficiency. Other symptoms, suggestive of growth hormone deficiency like poor concentration and low self esteem were not observed in our patients. Two patients had low Insulin growth factor 1 (IGF-1) suggestive of growth hormone deficiency. The rest of the patients had normal age and sex matched values for IGF-1 (Table 2).

Table 2: Biochemical screening for growth hormone deficiency of mild traumatic brain injury patients

Patient	Age (yr)	IGF-1 (ng/mL)	IGF-1(ng/mL) age matched normal range
ED	25	73	116-358
CM	43	191	101-267
RA	23	110	116-358
JV	28	135	117-329
RC	24	136	115-358
JD	21	155	116-358

B. Thyroid hormone deficiency.

The six patients did not manifest with any signs of hypothyroidism; bradycardia, facial puffiness, delayed deep tendon reflexes sweating, dry and coarse skin, slow movement and slow speech were not observed in any of them. The most common symptoms found were weight gain (83%) and decreased vigor (83%), which was noted in five of the six patients examined. Half of the patients claimed they had noted impaired memory. A third of the patients complained of muscle weakness and cold intolerance. Paresthesias, hoarseness and hearing problems were not manifested by any of the patients. Thyroid function tests were normal for all of the patients (Table 3).

Table 3: Biochemical screening for thyroid hormone deficiency of mild traumatic brain injury patients

PX	FT4 (ng/dL)	TSH (μIU/mL)
ED	1.49*	2.76†
CM	1.30	0.57
RA	1.60	1.81
JV	1.80	1.04
RC	1.40	1.89
JD	1.20	1.29

*Normal values= 0.8-1.9 ng/dL, † = 0.4-4 μIU/mL

C. Glucocorticoid deficiency

Orthostatic hypotension was not seen in any of the patients. The most common symptom was decreased vigor expressed by five patients (83%). A third of the patients expressed muscle weakness. One patient claimed to have decreased libido and erectile dysfunction. No weight loss, nausea and vomiting in stressful situations, or thinning of axillary and pubic hair were observed in any of the patients. The 8 a. m. cortisol levels were equivocal for five of the six patients (83%). However, confirmatory ACTH stimulation revealed an adequate adrenal response with 250 ug of cosynthropin (Table 4).

Table 4: The 8 am and ACTH stimulated cortisol levels of mild traumatic brain injury patients

PX	8 am Cortisol (µg/dL)	ACTH Stimulated Cortisol (µg/dL)
ED	14.48*	22.98†
CM	7.48	39.36
RA	15.81	36.06
JV	29.52	---
RC	16.58	49.97
JD	16.83	53.63

*Normal values: >5 µg/dL, † ≥ 18µg/dL

D. Sex hormone deficiency

None of the six patients manifested with gynecomastia or decreased body hair as signs of testosterone deficiency. As previously mentioned, five patients (83%) manifested with decreased vigor and half had impaired memory. Only one patient complained of decreased libido and erectile dysfunction. No other symptoms of male sex hormone deficiency, such as depression, thinning of hair (facial, axillary, pubic) and decreased exercise tolerance were observed. One patient (17%) had low testosterone levels associated with low leutinizing hormone levels that is consistent with hypogonadotrophic hypogonadism. Another patient had low FSH levels but adequate testosterone levels/result (Table 5).

Table 5: Biochemical evaluation of sex hormone deficiency of mild traumatic brain injury patients

PX	FSH (mIU/mL)	LH (mIU/mL)	Testosterone (ng/dL)
ED	3.80*	8.14†	844‡
CM	6.10	2.42	755
RA	<0.10	4.38	445
JV	0.80	2.11	501
RC	5.33	1.15	251
JD	2.93	2.53	379

*Normal values: 0.7-11.1 mIU/mL, † 1.57-8.71 mIU/mL; ‡ 280-800 ng/dL

Overall 3 of the 6 patients had a single abnormal axis, none had multiple or panhypopituitarism. None of the patients manifested with polyuria or dehydration, symptoms usually consistent with diabetes insipidus and posterior pituitary dysfunction. Table 6 summarizes the clinical manifestations of mild TBI patients a year after the event while table 7 presents their hormonal profile (Table 6).

Table 6: Summary of clinical manifestations of mild traumatic brain injury patients a year after the event

Clinical Manifestation	Frequency	%
Decreased vigor	5	83
Weight gain	5	83
Impaired memory	3	50
Cold intolerance	2	33
Decreased exercise capacity	2	33
Muscle weakness	2	33
Social isolation	2	33
Decreased libido	1	17
Erectile dysfunction	1	17

Table 7: Hormonal profile of mild TBI patients a year after the event

P	IGF-1 (ng/mL)	FT4 (ng/dL)	TSH (µIU/mL)	Cortisol (µg/dL) (8amACTH stimulated)	LH (mIU/mL)	FSH (mIU/mL)	Testosterone (ng/dL)
ED	73	1.49	2.76	14.48/22.98	8.14	3.80	844
CM	191	1.30	0.57	7.48/39.36	2.42	6.10	755
RA	110	1.60	1.81	15.81/36.06	4.38	<0.10	445
JV	135	1.80	1.04	29.52/ND*	2.11	0.80	501
RC	136	1.40	1.89	16.58/49.97	1.15	5.33	251
JD	155	1.20	1.29	16.83/53.63	2.53	2.93	379
Normal values	116-358† ng/mL	0.8 to 1.9 ng/dL	0.4 to 4 µIU/mL	> 5/18 µg/dL	1.57-8.71 mIU/mL	0.7-11.1 mIU/mL	280-800 ng/dL

*ND = Not done, † Age: 21-25y (116-358), 26-30 (117-329.0) 41-45(101-267.0), age & sex matched.

Discussion

Traumatic brain injury is the leading cause of death and disability in young adults more commonly among males. International data indicates vehicular accidents cause half of the cases, while a third were caused by falls and a fifth by violence related head injury.[10] Our data was compatible with available literature. Incidentally, we found that half of those who had mild traumatic brain injury patients underwent some form of invasive surgery on succeeding hospital days. This is a point of interest since most of the available data are based on postresuscitation Glasgow coma scale as stated by a review article.[6] Our data shows that initial assessment may dramatically change with time thus the effects of traumatic brain injury should be viewed not only as a point in time but rather a continuing phenomenon that may potentially deteriorate.

The manifestations of hypopituitarism may not be evident at any time after the accident[11] and the onset of hypopituitarism is not related to the severity of trauma.[12] A review by Benvega et al. reported a male to female ratio of 5:1 particularly in the age group between 11-29 years old mostly due to motor vehicular accidents.[11] This ratio approaches parity with aging owing to the increased likelihood of TBI caused by falls, for which members of both sexes have similar risks in later life.[1]

Overall prevalence's of hypopituitarism for mild TBI was 16.8%, moderate TBI 10.9% and severe TBI 35.3%. However, in some studies no associations of hypopituitarism with age, sex and severity of the TBI were reported.[4] Our study showed that 50% of the patients had an anterior pituitary hormone deficiency which is consistent with the 15 to 69% range of post-TBI hypopituitarism reported.[10]

The negative consequences of TBI in the quality of life include altered sleep, increased emotional reactions, decreased energy and physical mobility. Increased BMI, waist circumference, total and abdominal fat mass, were among the metabolic consequences noted.[13] The subtle clinical manifestations of partial hypopituitarism may be confused with the symptoms frequently reported by patients after a TBI, making biochemical diagnosis mandatory to establish a true record of the prevalence of hypopituitarism.[14]

Risk factors for posttraumatic hypopituitarism include, moderate to severe TBI, basal skull fractures, intracranial hemorrhage, diffuse axonal injury, increased intracranial pressure and prolonged stay in the intensive care unit.[6,15] Aimaretti et. al. (2003) pub-

lished data indicating TBI and subarachnoid hemorrhage as conditions at high risk for hypopituitarism showing impaired pituitary function in 37.5% (4% panhypopituitarism, 6% multiple and 25% isolated) of patients with subarachnoid hemorrhage and 35% (10% multiple and 27.5% isolated) in traumatic brain injury patients.[16] All of the patients included in this study had intracranial hemorrhage affecting various parts of the brain and increased intracranial pressure warranted emergency decompressive cranial surgeries. Our series showed half of these patients had isolated pituitary hormone abnormality.

The principal mechanisms of TBI are classified into focal brain damage due to contact injury types resulting in contusion, laceration and intracranial hemorrhage or diffuse brain damage due to acceleration/deceleration injury types resulting in diffuse axonal injury or brain swelling.[17] Fatal TBI was associated with various degrees of pituitary hemorrhagic infarctions present in more than 70% of patients while hypothalamic microhemorrhages were present in at least 40% of patients.[18]

Post-traumatic hypopituitarism is under diagnosed because of nonspecific signs and symptoms of pituitary hormone deficiency and clinical features may go undetected or mistaken for or masked by initial traumatic injury itself. Mild TBI is much more difficult to define and is likely to be under diagnosed. This can occur following acceleration-deceleration forces without direct trauma and often without explicit loss of consciousness.[19]

Earlier studies by Kelly in 2000 established that somatotroph and gonadotrope deficiencies were the most common and this holds true for most of the more recent works on traumatic brain injury.[20] This phenomenon was explained with the location of the somatotroph in the lateral wings of the anterior lobe and gonadotropes in the pars distalis and pars tuberalis which are located the in the vulnerable vascular territory of the long hypophyseal portal system. The corticotrophs and thyrotropes are largely found in the anteromedial portion of the gland in the protected territory of the short hypophyseal system.

Although preliminary studies done in the acute phase of traumatic injury reveal a predominantly somatotrophic and gonadotrophic hormone secretion abnormality, two follow-up studies revealed a change in the hormonal profile a year after the initial tests.[9,21] Possible mechanism includes recovery of pituitary function over time suggesting the presence of an effective repair mechanism for hypothalamus-pituitary damage.[7] Antipituitary antibodies may be associated with TBI-induced pituitary dysfunction, suggesting autoimmune mechanisms contributing to the development of hypopituitarism.[22]

Adrenal insufficiency in the acute phase is a serious life threatening complication that should be considered particularly in vasopressor dependent moderate to severe traumatic brain injury. These are patients with relative adrenal insufficiency that may warrant steroid replacement therapy.[23] In our patients however there was no endocrine evaluation for any of the patients at the acute phase.

In growth hormone deficiency (GHD) there is an increase in visceral fat and a decrease in muscle mass resulting in poor exercise performance and a decrease in bone density. This is linked to an overall increase in several cardiovascular risk factors. Symptoms include reduced vigor and concentration associated with low quality of life. Other studies revealed adverse lipid profile, an unfavorable body-composition, and a worsened perceived overall health related quality of life including a lowered energy level, worsened sleep and increased social isolation.[13]

Laboratory diagnosis for GHD is determined by dynamic endocrine testing because growth hormone has a fast half-life.[24] The use of IGF-1 is a useful indicator for GH deficiency and age adjusted normal ranges are available. A cut off of < 127.1 μg/L provided a sensitivity of 85% and a specificity of 68% for GHD patients. Values less than 77 μg/L had a very high probability of growth hor-

mone deficiency.[8] The insulin tolerance test remains the gold standard for the diagnosis of GHD but it is labor intensive and has potential risks. All the other stimulation tests require reagents that are not available in our setting. Further testing is needed to confirm growth hormone deficiency suspected in two of the subjects.

The clinical manifestations of secondary thyroid hormone deficiency are similar to primary hypothyroidism. Cold intolerance, constipation, fatigue and mental dullness are symptoms noted. Physical signs of bradycardia, hypothermia, slow speech and prolonged deep tendon reflexes may be present in patients with hypothyroidism. Only three signs, slow ankle reflex, puffiness and slow movements, have a positive predictive value greater than 90% for hypothyroidism.[25] Most of the studies on post-traumatic brain injury hypopituitarism show that TSH deficiency was relatively uncommon. This mainly because of the position of the thyrotropes, which are, located within the adenohypophysis in the protected territory of the short hypophyseal vessels.[9]

Elevated cortisol levels associated with increased ACTH release during the initial phase of trauma have been reported and there was a positive correlation between the severity of injury and cortisol levels in patients with mild or moderate TBI only.[1] Glucocorticoid insufficiency is associated with a variety of physical and emotional disturbances and early recognition of adrenocaortical function may positively affect the recovery of TBI patients. However, primary and secondary adrenal failure detected in the early period may be reversible.[23] Tanriverdi et al. revealed higher cortisol levels during the acute phase of the injury of post TBI patients compared to the levels a year after in their subjects.[7] Lieberman et. al. (2001) showed 46% of the subjects had abnormal basal cortisol results, the clinical significance of which finding remains to be determined.[2]

Clinical manifestations of chronic adrenal insufficiency include the following symptoms: Weakness, tiredness, fatigue, anorexia, gastrointestinal symptoms, postural dizziness and muscle and joint pains. Signs of adrenal insufficiency include weight loss, hypotension, hyperpigmentation and vitiligo.

Androgen deficiency can manifest with decrease in axillary and pubic hair, reduced muscle mass and infertility. Symptoms include decreased exercise tolerance, loss of libido and erectile dysfunction. Estrogen deficiency has signs of breast and vaginal atrophy, menstrual disturbances and perioral and periocular skin changes.[26]

Pituitary dysfunction following traumatic brain injury occurs in much higher frequency and raises the important question about potential contribution to the morbidity and mortality associated with head injuries.[10] In the light of established facts that onset of hypopituitarism does not correlate with severity, age and sex, the likelihood of under diagnosis is still possible,[4] Majority of the studies include the moderate to severe TBI with very few mild TBI, present recommendations regarding patients with symptomatic mild TBI as well as moderate to severe TBI as the groups that are at high priority for pituitary assessment.[10] In our series of patients it was observed that a year after their mild traumatic injury clinical symptoms suggesting hypopituitarism were present in 5 of the 6 patients. These symptoms were however, vague and non-specific. This is consistent with most available data on posttraumatic brain injury hypopituitarism. In a systematic review, signs and symptoms of hypopituitarism were pointed out to be subtle and often overlap with neurological and psychiatric sequelae of head trauma and subarachnoid hemorrhage.[6]

Biochemical hormonal testing done on the subjects did reveal isolated anterior pituitary hormone deficiencies but with signs and symptoms inconsistent with the deficient hormone. Growth hormone deficiency after a year is consistent with the studies of Tanriverdi et al. and Aimaretti et al. while LH/FSH deficiency was similar to the finding of Schneider et al.[7,12,27] Both are considered

as the most commonly affected anterior pituitary axes after traumatic brain injury.

As explained by Uberti from Italy, at the 2008 Endocrine Society in San Francisco, the occurrence of hypopituitarism should be seen as a spectrum of clinical signs and symptoms that are overt or subclinical, transient or permanent and partial or complete.[28] Thus, all head injuries should be taken seriously. However, the cost of biochemical testing to assess for hypopituitarism is expensive and the exact timing of the testing remains to be established. Present recommendations support screening for moderate to severe traumatic brain injury and symptomatic mild TBI.[10]

To conclude the most common symptoms of hypopituitarism noted a year after mild traumatic brain injury were weight gain & decreased vigor. No signs of hypopituitarism were noted. Abnormalities in the somatotrophic and gonadotrophic axes were found on biochemical pituitary hormone screening.

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