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## CHRONIC HYPOPHYSECTOMY AFTER TRAUMATIC BRAIN INJURY: RISK ASSESSMENT AND RELATIONSHIP TO OUTCOME

**OBJECTIVE:** Chronic pituitary dysfunction is increasingly recognized as a sequela of traumatic brain injury. We sought to define the incidence, risk factors, and neurobehavioral consequences of chronic hormonal deficiencies after complicated mild, moderate, or severe traumatic brain injury.

**METHODS:** Patients aged 14 to 80 years were prospectively enrolled at the time of injury and assessed at 3 and 6 to 9 months after injury for hormonal function and neurobehavioral consequences. Major and minor (subclinical) hormonal deficiencies, including growth hormone deficiency (GHD) and growth hormone insufficiency (GHI), were identified. Acute injury characteristics, neurobehavioral, and quality of life measures were compared in patients with and without major hormonal deficits by the use of multivariate analysis.

**RESULTS:** Out of 70 patients (mean age, 32 yr; median Glasgow Coma Scale score, 7; 19% women) tested at 6 to 9 months after injury, 15 (21%) had at least one major hormonal deficiency, 20 (29%) had minor deficiencies, and 30 (43%) had major and/or minor deficiencies. Patients with major deficiencies included 16% with GHD or GHI, 10.5% with hypogonadism, and 1.4% with diabetes insipidus. None of the patients required adrenal or thyroid replacement. At 6 to 9 months after injury, patients with major hormonal deficits had more abnormal acute computed tomographic findings ( $P = 0.014$ ), greater acute and chronic body mass index ( $P < 0.01$ ), and a worse Disability Rating Scale score (multivariate  $P = 0.04$ ). Compared with the 59 growth hormone-sufficient patients, the 11 patients with GHD or GHI had worse Disability Rating Scale scores (multivariate  $P = 0.04$ ), greater rates of depression, (90 versus 53%; multivariate  $P = 0.06$ ), and worse quality of life in the Short Form-36 domains of energy and fatigue (multivariate  $P = 0.03$ ), emotional well-being (multivariate  $P = 0.02$ ), and general health (multivariate  $P = 0.07$ ).

**CONCLUSION:** Chronic hypopituitarism warranting hormone replacement occurs in approximately 20% of patients after complicated mild, moderate, or severe traumatic brain injury and is associated with more severe brain injuries and increased disability. GHD and GHI are also associated with increased disability, poor quality of life, and a greater likelihood of depression. The clinical significance of minor hormonal deficits, which occur in almost 30% of patients, warrants further study. Given that major deficiencies are readily treatable, routine pituitary hormonal testing within 6 months of injury is indicated for this patient population.

**KEY WORDS:** Endocrinopathy, Growth hormone deficiency, Hypopituitarism, Injury severity, Pituitary failure, Traumatic brain injury

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**T**raumatic brain injury (TBI) remains a leading cause of mortality and morbidity worldwide and is still a major cause of disability among children and young adults in

the United States (1, 4). A majority of survivors of moderate or severe TBI have residual neurobehavioral (NB) deficits, depression, and/or poor quality of life (QOL) (1, 32, 42, 49, 53, 56,

59, 73). One hypothesis receiving much attention is that TBI-induced hypothalamic-pituitary dysfunction may contribute to poor QOL in many TBI survivors. Given the pituitary gland's confinement within the sella and tethering to the hypothalamus by the infundibulum, the neuroendocrine axis is susceptible to primary mechanical insults and secondary insults from hypotension, hypoxia, anemia, and brain swelling (25, 26, 28, 29, 51, 55).

Several recent cohort studies, including our own, have documented long-term hormonal dysfunction after moderate or severe TBI. Collectively, these studies indicate that 25 to 40% of such TBI patients will develop chronic hormonal deficiencies, with the somatotroph and gonadotroph axes being most commonly affected and the thyrotroph and corticotroph axes being affected less frequently (5, 7, 9, 10, 21, 51, 58, 60, 74). Although these studies have added to our understanding of posttraumatic pituitary failure, they have not clearly delineated patient-specific or TBI-related risk factors for hormonal loss, and few studies have followed the patients longitudinally from the acute injury phase through the chronic postinjury phase. Additionally, with the exception of our recent report showing that TBI patients with chronic growth hormone (GH) insufficiency (GHI) had higher rates of depression and worse QOL, the relationship between hormonal loss and long-term NB deficits has not been well-established (52).

In this prospective longitudinal study, patients were enrolled acutely after injury; pituitary function was studied at 3 months and again at 6 to 9 months after injury. We report the rates and associated risk factors of long-term pituitary hormonal dysfunction in this cohort of adolescent and adult TBI patients and compare NB and QOL outcomes in patients with and without hormonal dysfunction. We hypothesized that: 1) acute prognostic indicators of TBI injury severity would be predictive of long-term pituitary dysfunction, and 2) increasing rates of hypopituitarism would correlate with worse NB deficits and a reduced QOL. To test these hypotheses, patients in the chronic phase after moderate or severe TBI underwent anterior and posterior pituitary function testing. Anterior pituitary hormonal deficits were arbitrarily categorized before data analyses as major if the deficiencies warranted hormone replacement therapy and were considered minor (subclinical) if they did not.

## PATIENTS AND METHODS

The institutional review boards of each participating medical center approved this study. In the acute injury phase, informed proxy consent was obtained from legal authorized representatives within 96 hours of admission to the University of California at Los Angeles (UCLA) and University of California at Davis Medical Centers and within 72 hours of admission to Harbor-UCLA Medical Center. Patients personally consented for study participation in the chronic phase (3–9 months after TBI) before pituitary stimulation and neurobehavioral tests.

Enrollment criteria for this prospective longitudinal follow-up study included: 1) age 14 to 80 years and admission to the intensive care unit (ICU) of one of three Level 1 trauma centers within 24 hours of injury, 2) an initial head computed tomographic (CT) scan showing acute intracranial hemorrhage, and 3) a postresuscitation Glasgow Coma Scale (GCS) score of 3 to 14 or a deterioration to a GCS score of 14 or less within 24

hours of admission. Patients were further categorized as sustaining a complicated mild TBI (GCS 13–14 with intracranial hemorrhage on acute CT scans), moderate TBI (GCS 9–12), or severe TBI (GCS 3–8) (22, 86). Patients who achieved a Glasgow Outcome Scale-Extended (GOS-E) category of lower severe disability or higher at 6 to 9 months after injury participated in neurobehavioral testing. Patients were excluded if they were pregnant, had cancer, autoimmune deficiency syndrome, severe neurological or psychiatric illness, preexisting adrenal or pituitary insufficiency, or had received glucocorticoids within 3 months of injury.

Patients were admitted to the ICU after stabilization or after craniotomy for intracranial hematoma evacuation. Patient management was performed in accordance with the "Guidelines for the Management of Severe Head Injury" (23), including an algorithm for maintaining intracranial pressure (ICP) less than 20 mmHg and cerebral perfusion pressure (CPP) greater than 60 to 70 mmHg.

### Healthy Control Cohort and Definition of Hormonal Insufficiency

Healthy volunteers were recruited by advertisements posted at Harbor-UCLA and UCLA Medical Centers to undergo pituitary hormonal stimulation testing as described herein. Volunteers with previous diagnoses of endocrine diseases, currently on hormone replacement therapy, and pregnant women or those on birth control pills for the past 3 months were excluded. Detailed description of these volunteers was previously reported (76). Although not studied at the same phase of the menstrual cycle, all women reported a history of regular menses.

### Anterior and Posterior Pituitary Hormonal Testing

Hormonal evaluations were performed once in healthy volunteers and on up to two occasions in TBI patients at 3 months and again at 6 to 9 months after injury in the General Clinical Research Center of their respective hospitals. Testing was performed between 8 AM and 12 PM after an overnight fast. Pituitary stimulation testing and NB and QOL testing were deferred up to 9 months after injury in some TBI patients as the result of logistical and ongoing recovery issues that precluded testing at the 6-month time-point.

The following hormonal tests were performed after baseline blood draws at –30 minutes and time zero: 1) growth hormone-releasing hormone (GHRH)-arginine stimulation test to assess somatotroph function (11, 12, 38, 76); 2) low-dose cosyntropin stimulation test to assess corticotroph function (2, 96); 3) gonadotropin-releasing hormone (GnRH) stimulation test to assess gonadotroph function, by measuring both luteinizing hormone (LH) and follicle stimulating hormone (FSH); 4) measurements of free thyroxine (free T4), total thyroxine (T4), and thyroid-stimulating hormone (TSH) for thyrotroph function; and 5) measurements of prolactin to assess lactotroph function. Immediately after a time 0 blood draw, a 30-minute arginine infusion (30 g over the course of 30 min) was started, and injections of GHRH (1 µg/kg), Cortrosyn (1 µg), and GnRH (100 µg intravenously) were given. Blood draws were then performed at 15, 20, 30, 60, 90, and 120 minutes for the anterior pituitary hormone measurements and their target hormones. We assessed posterior pituitary function by obtaining urine sodium, osmolality within the hour before time zero and serum sodium, blood urea nitrogen, creatinine, osmolality, and arginine vasopressin at time zero. Diabetes insipidus (DI) was defined as a urine specific gravity of 1.005 or less, urine osmolality less than 500 mOsm/kg, and serum osmolality greater than 290 mOsm/kg.

Serum and urine samples for all hormones from control and TBI patients were stored at –20°C before assay and then measured in the GCRC Core Laboratory of Harbor-UCLA Medical Center using previously published validated methods (75, 76). The reference ranges

expressed as the 5th and 95th percentile for healthy adult men and women are provided in *Table 1*: adrenocorticotrophic hormone (ACTH), baseline and peak cortisol, TSH, total T4, free T4, peak LH and FSH, total testosterone, estradiol, prolactin, and peak GH.

Major anterior hormonal deficiencies were defined as follows: corticotroph axis-peak cortisol below the 5th percentile; thyrotroph axis-T4 and free T4 below the 5th percentile; gonadotroph axis-total testosterone below the 5th percentile (men) and serum estradiol below the 5th percentile with co-existing menstrual disturbances (women). For the somatotroph axis, because the definition for adult-onset GH deficiency remains somewhat controversial (12), we defined GH-secretory capacity at two cut-points of GH deficiency (GHD) and GHI, which correspond to the 5th and 10th percentiles of peak GH in response to GHRH-arginine stimulation (11, 38, 76). Persistent DI was also considered a major hormonal dysfunction.

Minor (subclinical) deficiencies included corticotroph axis-ACTH below the 5th percentile or baseline cortisol below the 5th percentile; thyrotroph axis-low free T4 but normal T4 or vice versa (low defined as below the 5th percentile); gonadotroph axis-peak or baseline LH or FSH below the 5th percentile with normal total testosterone (men) or normal menstruation (women); somatotroph axis-IGF-1 below the 5th percentile of the age appropriate ranges; and lactotroph axis-prolactin above the 95th percentile.

**TABLE 1. Normal hormonal reference range from healthy men and women<sup>a</sup>**

Hormonal axis	5th percentile	95th percentile	Mean
Peak GH <sup>b,c</sup> (ng/mL)	12.1 (10th percentile)	140	29.8
Baseline cortisol (ng/dL)	4.5	15.6	8.4
Peak cortisol (ng/dL) <sup>c</sup>	12.0	25.7	17.6
Free T4 (ng/dL)	0.8	2.0	1.2
Testosterone (ng/dL)	298	811	492
Estradiol (pg/mL)	27.6	159	66
Peak FSH <sup>c</sup> (males) (IU/L)	2.1	17	6.0
Peak FSH <sup>c</sup> (females) (IU/L)	2.7	25.4	8.2
Peak LH <sup>c</sup> (males) (IU/L)	4.7	54.1	16.0
Peak LH <sup>c</sup> (females) (IU/L)	8.1	128	32.2
Prolactin (males) (ng/mL)	3.0	15.4	6.9
Prolactin (females) (ng/mL)	5.6	24.3	11.7
IGF-1 (by age) (ng/mL)			
Age 12–15 yr (males)	229	845	440
Age 12–15 yr (females)	128	437	237
Age 16–20 yr	205	694	377
Age 25–39 yr	128	437	237
Age 40–54 yr	101	322	180
Age 55 yr and older	80	259	143

<sup>a</sup> GH, growth hormone; T4, thyroxine; FSH, follicle-stimulating hormone; LH, luteinizing hormone; IGF-1, insulin-like growth factor-1; DRS, Disability Rating Scale. A detailed description of these controls has been reported previously (76).

<sup>b</sup> For Peak GH, the 10th percentile cut-off was used (5th percentile is 6.0 ng/mL).

<sup>c</sup> Peak hormone levels after combined anterior pituitary test.

## Neurobehavioral and QOL Testing

All patients underwent NB and QOL testing between 6 to 9 months after injury and within 2 weeks of undergoing pituitary stimulation testing. As previously described (52), testing was performed in a quiet setting over a 2- to 3-hour period at one of the participating medical centers. The neuropsychologist performing the tests had no knowledge of the patients' hormonal status.

The NB testing battery assessed the five domains of memory, concentration, depression, anxiety, and fatigue (24, 66, 67, 77, 78, 82). These specific domains were selected because the result of previous studies indicate that such deficits often persist after TBI and in patients with adult-onset GHD (15–17, 30, 31, 42, 59, 79, 89). Scores for each specific test within the five NB domains were recorded as either above or below the threshold for abnormality in that domain. For example, if any of the three tests administered to assess for depression were abnormal, a patient was classified as having depression. From these scores, a total number of NB deficits (range, 0–5) was calculated with one point given for any abnormal test in each of the five NB domains.

Two QOL measures were also performed, including the QOL-Assessment of GHD in Adults (AGHDA), which uses a 20-point scale, and the Short Form-36 Health Survey (SF-36), which is used to test eight "health concepts" and has a 0- to 100-point scale (20, 37, 54, 61, 68, 69, 92). Additional global outcome measures included the eight-point GOS-E and the Disability Rating Scale (DRS), which uses a 30-point scale (87, 90, 93, 94).

Neurobehavioral and QOL testing results reported here include only those performed before hormone replacement therapy was instituted. If the subjects had any major anterior hormone deficiencies, these were replaced to restore normal levels before retesting for GH deficiency and repeat neurobehavioral testing.

## Injury Characteristics Potentially Associated with Hormonal Dysfunction

### Clinical Parameters

Age, postresuscitative GCS score, postresuscitative pupillary status (both normal, one abnormal, both abnormal), Injury Severity Score (ISS), length of ICU stay, and 6- to 9-month GOS-E score were recorded for each patient (47).

### Ischemia Factors

Factors associated with possible ischemic insult to the hypothalamic-pituitary axis included hypotension (systolic blood pressure < 90 mmHg) or severe anemia (hematocrit < 25%) during the patients' ICU stay or hypoxia (PaO<sub>2</sub> < 60 mmHg, S<sub>a</sub>O<sub>2</sub> < 90%, within 24 h of injury, or agonal respirations or apnea in the field) (14, 26, 48, 63, 70). As we recently described (27), an ischemia score ranging from 0 to 3 was also calculated for each patient with one point each for hypotension, hypoxia, or severe anemia.

### CT Findings

The following findings of intracranial injury, all of which have been associated with worse outcome after TBI, were recorded from patients' first and second CT scans obtained within 24 hours of injury: midline shift of more than 4 mm, basilar cistern compression, diffuse brain swelling, evacuated acute subdural hematoma, evacuated intracerebral hematoma, multiple contusions, subarachnoid hemorrhage, hypothalamic hemorrhage or swelling, diffuse punctuate (subcortical) hemorrhage (consistent with shearing injuries), and cranial fractures (calvarial, cranial base, sphenoid, or facial) (35, 40, 57, 88). An aggregate

CT score from 0 to 10 was calculated for each patient, with one point for each of the aforementioned findings.

*ICP, CPP, and Blood Pressure*

For patients in whom an ICP monitor was placed, mean and maximal ICP and CPP, total hours ICP greater than 20 mmHg, and total hours CPP less than 50 mmHg were recorded (48, 63–65, 81). The hourly mean arterial pressure was also recorded.

*Acute Adrenal Insufficiency and DI Status*

During the acute phase, patients were categorized as to whether or not they developed acute adrenal insufficiency (AI) based on serial serum cortisol blood draws (27). Patients were defined as having AI if two consecutive cortisol levels were 15 µg/dL or less or one cortisol level was less than 5 µg/dL. Patients were categorized as having acute AI if they had a urine specific gravity of 1.005 or less with urine output greater than 300 mL/hour for 2 hours or more and treated with desmopressin acetate. These patients were then referred to an endocrinologist to determine whether long-term hormone replacement was needed.

*Body Mass Index (BMI) Calculations*

BMI was calculated after injury based on patients' height and weight taken within 24 hours of injury. The BMI was recalculated at the time of stimulation testing 6 to 9 months postinjury. Changes in baseline (acute) BMI and at 6 to 9 months were compared between GHD and GHI patients and those with GH-sufficiency

*Data Analysis*

At the 3- and 6 to 9-month time points, patients were categorized as being deficient in one or more hormonal axes at the 5th percentile cut-off points. Comparisons were then made of change in hormonal deficiency rates at the 3- and 6 to 9-month time points and of patients with any hormonal deficiency versus no deficiency at 6 to 9 months after injury. NB and QOL outcomes at 6 to 9 months after injury were compared in patients with and without major hormonal dysfunction. Data with approximately normal distributions are summarized with mean ± standard deviation. Data with skewed distributions (i.e., age, GCS, ISS, CT score, duration of ICU and hospitalization, total number NB deficits) are summarized with percentiles. For comparison of major hormonal deficiency versus no major hormonal deficiencies or of GHD or GHI versus no GHD or GHI the following tests were used: the Mann-Whitney test for interval and continuous variables and Fisher's exact test for percentages. To determine whether hormonal status (major hormonal deficiency or GHD or GHI) was independently predictive of outcome, multivariate analyses were performed with multiple linear regression to control for the outcome predictors of patient age, GCS, pupillary status, presence of hypotension, and CT score (26, 40, 42, 48, 63, 64, 65). A multivariate *P* value was shown for every univariate *P* value less than 0.10. As a result of the small sample sizes, it was necessary to control only for a subset of these predictors; optimal subsets were chosen using the adjusted *R*<sup>2</sup> criterion.

**RESULTS**

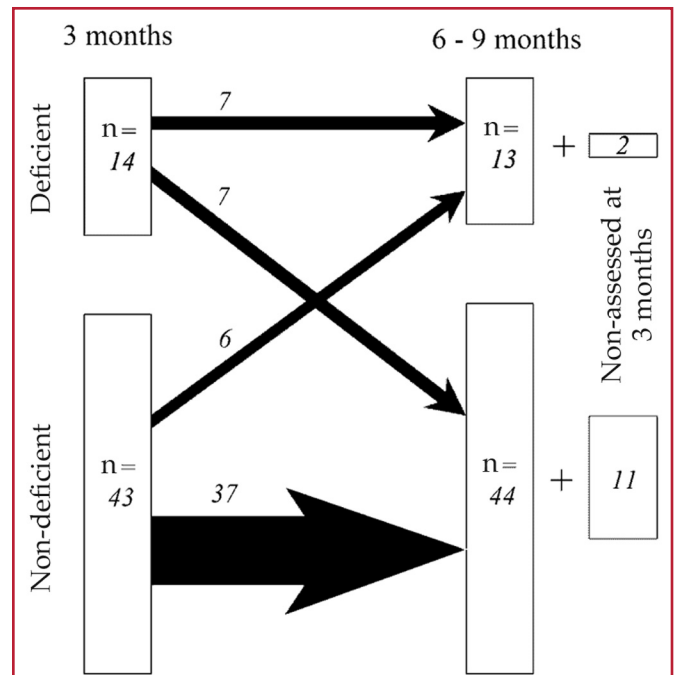
**Patient Enrollment and Follow-up**

Between June 2002 and January 2006, 204 patients were enrolled acutely into the study, and two additional patients were enrolled within 3 months of TBI. During the acute phase

of the study, a total of 45 (22%) patients died, and 11 (5%) others were excluded because they received high-dose glucocorticoids (*n* = 7) or had previous confounding medical conditions (*n* = 4). During the chronic phase of the study, 21 (10%) patients were lost to follow-up before the 6-month postinjury time point and 55 (27%) could not be recontacted, failed to return for pituitary function and neurobehavioral testing, or had medical conditions that precluded stimulation testing. Four (2%) patients had only minimal participation in the neurobehavioral testing and were excluded. The final number of patients with complete data at 6 to 9 months after injury was 70 patients: 34% of the total patients enrolled acutely (*n* = 206) or 47% of patients who survived and were not excluded during the acute injury phase because of glucocorticoid administration or prior medical conditions (*n* = 150).

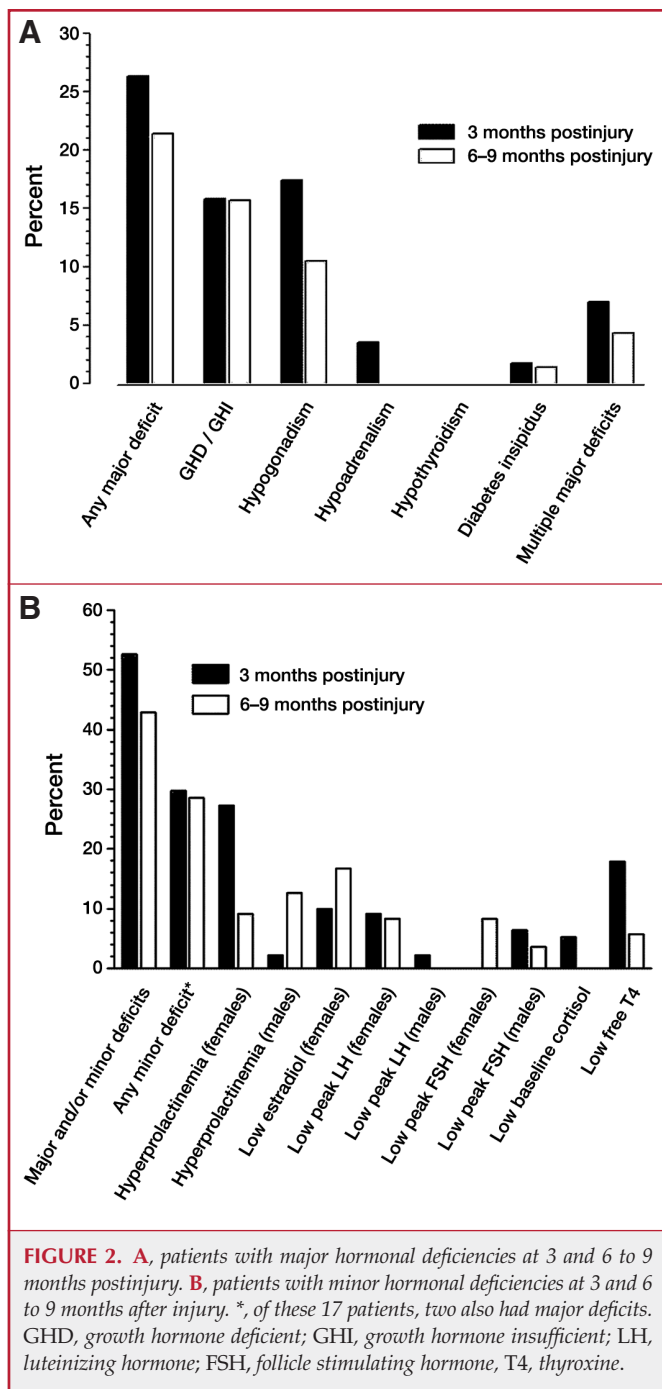
**Rate of Hormonal Deficiency at 3 Months and 6 to 9 Months After Injury**

Of the 70 patients who had testing at 6 to 9 months after injury, 57 patients also had testing at 3 months after injury. As shown in Figure 1, 14 (25%) of 57 patients at 3 months and 15 (21%) of 70 at 6 to 9 months were diagnosed with major hormonal deficits in the somatotroph, gonadotroph, thyrotroph, corticotroph, or posterior pituitary axes. Of the 14 patients with major hormonal deficits at 3 months after injury, seven (50%) persisted with major



**FIGURE 1.** Changes in major hormonal deficiencies in 57 patients tested at 3 months and 6 to 9 months after injury. Of the 14 patients with major deficiencies at 3 months, 50% recovered at 6 to 9 months; of the 43 without major deficiencies at 3 months, 14% developed new major deficiencies. A total of 13 additional patients were tested at 6 to 9 months, including two with and 11 without major deficiencies.

deficiencies at 6 to 9 months after injury, whereas seven (50%) recovered (two from adrenal insufficiency, four from testosterone deficiency, and three from GH-deficiency). Of the 43 patients (75%) who were nondeficient or had subclinical deficiencies at 3 months after injury, six (14%) patients developed new major hormonal deficits at 6 to 9 months (four developed GHD or GHI and two developed testosterone deficiency).



The major and minor hormonal deficiencies at 3 months and 6 to 9 months after injury are shown in Figure 2, A and B, respectively. At 3 months after injury, 14 (25%) had major deficiencies, 17 (30%) had minor deficiencies, and 30 (53%) had major and/or minor deficiencies. At 6 to 9 months after injury, testing in 70 patients revealed major deficiencies in 15 (21%), minor deficiencies in 20 (29%), and both major and minor deficiencies in five (7%). Overall, 30 (43%) had a major and/or a minor deficiency. At 6 to 9 months, major deficiencies included somatotroph (16%), gonadotroph (10.5%), corticotroph (0%), and thyrotroph (0%); permanent DI occurred in one patient (1.4%). Only two patients older than the age of 65 years were tested at 6 to 9 months after injury, and they had no deficiencies.

### Patient and Injury Characteristics

As shown in Table 2, the 15 patients with major hormonal deficiencies at 6 to 9 months after injury were similar to the 55 hormonally sufficient patients in terms of age, ISS (data not shown), GCS, pupillary changes, length of ICU and hospital stay, ischemia score, and ICP and CPP measures. One of these patients who sustained a complicated mild TBI did develop GHI at 6 to 9 months after injury. The presence of acute adrenal insufficiency and acute DI were also similar between groups. However, the patients with major hormonal deficiencies had a greater BMI acutely ( $P = 0.005$ ) and at 6 to 9 months after injury ( $P = 0.002$ ), and had more severe brain injuries based on CT findings ( $P = 0.014$ ). As shown in Table 3, those with major hormonal deficiencies had a greater occurrence of diffuse brain swelling ( $P = 0.017$ ) and evacuated ICH or multiple contusions ( $P = 0.017$ ).

### NB and QOL Comparisons

As seen in Tables 4 and 5, patients with major hormonal deficiencies had a worse global outcome by DRS (univariate  $P = 0.032$ ; multivariate  $P = 0.04$ ). In the SF-36, there was a trend for worse general health in patients with major hormonal deficiencies (univariate  $P = 0.048$ ; multivariate  $P = 0.12$ ).

### GH Deficiency/GH Insufficiency at 6 to 9 Months after Injury

As seen in Tables 6 and 7, the 11 patients (16%) with GHD or GHI were similar to the GH-sufficient patients in all acute injury parameters except acute CT findings and BMI. These 11 patients had an overall worse CT score compared with the 59 patients without GHD or GHI ( $P = 0.019$ ), with high rates of diffuse brain swelling (91%) and evacuated ICH or contusions (36%). The patients with GHD or GHI also had a greater BMI acutely ( $P = 0.001$ ) and at 6 to 9 months after injury ( $P = 0.001$ ).

Regarding long-term outcome (Table 8), patients with GHD or GHI had worse global outcome by DRS (univariate  $P = 0.068$ ; multivariate  $P = 0.04$ ). Patients with GHD or GHI also had a trend toward greater rates of depression, (90 versus 53%, univariate  $P = 0.037$ ; multivariate  $P = 0.06$ ) and a trend toward greater total number of NB deficits (univariate  $P = 0.055$ ; mul-

**TABLE 2. Risk factors in patients with or without major hormonal deficiencies at 6 to 9 months after injury<sup>a</sup>**

Characteristic	Major hormonal deficiency, n = 15 (21%)	No major hormonal deficiency, n = 55 (79%)	P value
Mean Age ± SD (range)	33 ± 16 (18–61)	31 ± 17 (14–76)	0.707
Male sex	14/15 (93%)	43/55 (78%)	0.272
Mean baseline (acute) body mass index ± SD	28.6 ± 3.8	24.9 ± 4.4	0.005 <sup>b</sup>
Mean 6–9 months body mass index ± SD	28.4 ± 5.8	24.3 ± 3.9	0.002 <sup>b</sup>
Median post-resuscitation Glasgow Coma Scale (range)	7 (3–15)	8 (3–15)	0.154
Abnormal pupils	7/15 (47%)	19/53 (36%)	0.550
Hypotension	9/14 (64%)	23/55 (42%)	0.148
Hypoxia	4/15 (27%)	7/52 (13%)	0.248
Anemia	4/14 (29%)	19/54 (35%)	0.758
Ischemia score (range)	1 (0–3)	1 (0–3)	0.395
Median computed tomography score (range)	5 (2–8)	3 (0–8)	0.014 <sup>b</sup>
<b>Acute hormonal changes</b>			
Acute adrenal insufficiency	6/14 (43%)	26/54 (48%)	0.772
Acute diabetes insipidus	1/15 (6.7%)	0/55 (0%)	0.214

<sup>a</sup> SD, standard deviation. Percentages are compared with the Fisher’s exact test. Interval measures are summarized as medians (range) and compared with the exact Mann-Whitney test. Continuous measures are summarized as means ± standard deviation and compared using the exact Mann-Whitney test or *t* test (age).

<sup>b</sup> Significant.

**TABLE 3. Computed tomographic findings in patients with or without major hormonal deficiencies at 6 to 9 months after injury<sup>a</sup>**

Acute computed tomographic finding	Major hormonal deficiency, n = 15 (21%)	No major hormonal deficiency, n = 55 (79%)	P value
Midline shift > 4 mm	3 (20%)	14 (25%)	1.000
Diffuse brain swelling	13 (87%)	28 (51%)	0.017 <sup>b</sup>
Hypothalamic swelling or hemorrhage	6 (40%)	9 (16%)	0.073
Effaced cisterns	8 (53%)	25 (45%)	0.771
SAH/suprasellar SAH	11 (73%)	31 (56%)	0.373
Evacuated subdural hematoma	1 (7%)	9 (16%)	0.678
Evacuated intracranial hemorrhage or contusion	4 (27%)	2 (4%)	0.017
Multiple contusions	10 (67%)	25 (45%)	0.244
Shearing injuries (deep punctuate hemorrhage)	5 (33%)	14 (25%)	0.531
Cranial or facial fracture	9 (60%)	22 (40%)	0.242
Median aggregate computed tomographic score (range)	5 (2–8)	3 (0–8)	0.014 <sup>b</sup>

<sup>a</sup> SAH, subarachnoid hemorrhage. Percentages are compared with the Fisher’s exact test. The interval measure is summarized as the median and compared using the exact Mann-Whitney test.

<sup>b</sup> Significant.

tivariate *P* = 0.06). As seen in Table 9, QOL was also worse in the GHD and GHI group compared with the GH-sufficient group in the SF-36 domains of limitations as the result of energy and fatigue (univariate *P* = 0.053; multivariate *P* = 0.03), emotional well-being (univariate *P* = 0.018; multivariate *P* = 0.02) and general health (univariate *P* = 0.001; multivariate *P* = 0.07).

## DISCUSSION

### Summary of Findings

In 70 patients with complicated mild, moderate, or severe TBI, 21% met the criteria for a major hormonal deficiency and 43% had major and/or minor deficiencies at a follow-up period of 6 to 9 months after injury. Of the patients tested at 3 months

**TABLE 4. Global and neurobehavioral outcome in patients with or without major deficiencies at 6 to 9 months after injury<sup>a</sup>**

Measure	Major hormonal deficiency, n = 15 (21%)	No major hormonal deficiency, n = 55 (79%)	P value
GOSE <sup>b</sup>	4.9 ± 1.3	5.6 ± 1.5	0.066 <sup>d</sup>
DRS <sup>c</sup>	4.3 ± 5.0	2.1 ± 2.4	0.032 <sup>e,f</sup>
<b>Memory</b>			
Buschke selective reminding, CLTR <sup>b</sup>	21.6 ± 11.8	24.4 ± 16.9	0.911
Rey complex figure <sup>b</sup>	14.0 ± 7.8	16.9 ± 8.3	0.367
Memory deficit present	12/14 (86%)	37/53 (70%)	0.320
<b>Concentration</b>			
Digit symbol, written <sup>b</sup>	37.4 ± 17.7	39.7 ± 15.0	0.242
Digit symbol, oral <sup>b</sup>	41.1 ± 14.4	47.3 ± 17.8	0.217
Concentration deficit present	9/14 (70%)	34/54 (63%)	1.000
<b>Depression</b>			
Neurobehavioral rating scale <sup>c</sup>	1.9 ± 0.7	1.7 ± 0.9	0.326
CES, depression <sup>c</sup>	12.5 ± 10.2	11.4 ± 11.0	0.401
Hospital anxiety, depression <sup>c</sup>	5.5 ± 4.3	3.6 ± 3.6	0.131
Depression deficit present	10/13 (77%)	28/54 (52%)	0.127
<b>Anxiety</b>			
Hospital anxiety <sup>c</sup>	3.8 ± 4.2	4.7 ± 3.8	0.331
Neurobehavioral rating scale, anxiety <sup>c</sup>	2.1 ± 2.1	1.8 ± 0.8	0.838
Anxiety deficit present	9/14 (64%)	30/54 (56%)	0.763
<b>Fatigue</b>			
Neurobehavioral rating scale, fatigue <sup>c</sup>	1.4 ± 0.6	1.3 ± 0.5	0.333
Fatigue deficit present	5/14 (36%)	13/54 (24%)	0.498
<b>Total no. of neurobiological deficits<sup>c</sup></b>	3 (1–5) (n = 14)	3 (0–5) (n = 54)	0.228

<sup>a</sup> GOSE, Glasgow Outcome Scale-Extended; DRS, Disability Rating Scale; CLTR, consistent long-term retrieval; CES, Center for Epidemiological Studies. Percentages are compared with the Fisher's exact test. Interval measures are summarized as medians (range) and compared using the exact Mann-Whitney test. Continuous measures are summarized as means ± standard deviation and compared using the exact Mann-Whitney test.

<sup>b</sup> Greater scores represent better health.

<sup>c</sup> Lower scores represent better health. Neurobehavioral tests were performed at 6 to 9 months after injury. Multivariate P values were derived by controlling for the best subset of predictors from age, Glasgow Coma Scale score, pupil status, hypotension, and computed tomographic score.

<sup>d</sup> Multivariate P value of 0.22 controlling for Glasgow Coma Scale.

<sup>e</sup> Multivariate P value of 0.04 controlling for Glasgow Coma Scale.

<sup>f</sup> Significant.

after injury, 50% with major deficiencies had resolution of their endocrinopathy by 6 to 9 months after injury; of the patients without major deficiencies at the 3-month time point, 14% developed new major deficiencies at 6 to 9 months after injury. Patients who developed long-term major hormonal deficits and who had GHD or GHI had more severe acute CT findings, indicating a greater degree of parenchymal brain injury. At 6 to 9 months after injury, the 15 patients with major hormonal deficiencies had, on average, worse disability as measured by the DRS. The subcohort of patients with GHD or GHI had worse DRS, greater rates of depression, and worse QOL compared with patients with normal GH function. This study is the first to demonstrate a relationship between TBI-induced chronic hypopituitarism, long-term disability, and QOL.

### Previous Studies on Posttraumatic Hypopituitarism

As shown in *Table 10*, previous cohort studies indicate the somatotroph and gonadotroph axes are most vulnerable to the primary and secondary insults of moderate and severe TBI, with deficiency rates averaging 16 and 14%, respectively. In contrast, corticotroph, thyrotroph, and posterior pituitary deficiencies are less common, with rates averaging 8, 5, and 2%, respectively (5, 7, 9, 10, 21, 43, 51, 58, 60, 74, 85). The overall rate of hypopituitarism in this study is somewhat lower than reported by others shown in *Table 10*, which may be related to differences in pituitary function testing and the normal reference ranges used. Additionally, our study had a high rate of patients lost to follow-up who were so severely

**TABLE 5. Quality of life in patients with or without major deficiencies at 6 to 9 months after injury**

Measure <sup>a</sup>	Major hormonal deficiency, n = 15 (21%)	No major hormonal deficiency, n = 55 (79%)	P value
QOL, AGHDA <sup>b</sup>	6.2 ± 6.5 (n = 13)	6.8 ± 6.5 (n = 53)	0.964
SF-36 <sup>c</sup>	n = 12	n = 54	
Physical functioning	72.9 ± 29.3	71.3 ± 30.7	0.962
Limitations due to physical health	45.8 ± 43.7	49.1 ± 43.2	0.829
Limitations due to emotional health	69.4 ± 46.0	80.2 ± 34.6	0.491
Energy and fatigue	57.1 ± 24.7	63.1 ± 24.2	0.447
Emotional well-being	68.7 ± 23.3	76.5 ± 22.5	0.181
Social functioning	63.5 ± 27.4	76.9 ± 26.9	0.101
Pain	70.2 ± 26.1	78.2 ± 22.6	0.304
General health	62.9 ± 20.5	75.1 ± 19.0	0.048 <sup>d,e</sup>

<sup>a</sup> QOL, quality of life; SF-36, Short Form -36; AGHDA, Assessment of Growth Hormone Deficiency in Adults. Continuous measures are summarized as means ± standard deviation, and compared using the exact Mann-Whitney test.

<sup>b</sup> Lower scores represent better health.

<sup>c</sup> Greater scores represent better health. Quality of life tests performed at 6–9 months after injury.

<sup>d</sup> Multivariate P value of 0.12, controlling for best subset of predictors (Glasgow Coma Scale and hypotension) from age, Glasgow Coma Scale, pupil status, hypotension, and computed tomographic score.

<sup>e</sup> Significant.

**TABLE 6. Risk factor analysis of growth hormone deficiency and growth hormone insufficiency versus growth hormone-sufficient patients<sup>a</sup>**

Characteristic	GHD/GHI, n = 11 (16%)	GH-sufficient, n = 59 (84%)	P value
Mean age ± SD (range)	34 ± 16 (18–61)	31 ± 17 (14–76)	0.579
Male sex	10/11 (91%)	47/59 (80%)	0.676
Mean baseline (acute) body mass index ± SD	29.9 ± 2.4 (n = 10)	24.9 ± 4.4	0.001 <sup>b</sup>
Mean 6–9 months body mass index ± SD	29.4 ± 4.8	24.4 ± 4.16	0.001 <sup>b</sup>
Median after resuscitation, Glasgow Coma Score (range)	7 (3–15)	7 (3–15)	0.358
Abnormal pupils	5/11 (45%)	21/57 (37%)	0.737
Hypotension	6/10 (60%)	26/59 (44%)	0.496
Hypoxia	3/11 (27%)	8/56 (14%)	0.367
Anemia	3/10 (30%)	20/58 (34%)	1.000
Ischemia score (range)	1 (0–3)	1 (0–3)	0.680
Median computed tomographic score (range)	5 (2–8)	3 (0–8)	0.019 <sup>b</sup>
Acute hormonal changes			
Acute adrenal insufficiency	5/10 (50%)	27/58 (47%)	1.000
Acute diabetes insipidus	0/11 (0%)	1/59 (2%)	1.000

<sup>a</sup> GHD, growth hormone deficiency; GHI, growth hormone insufficiency; GH, growth hormone; SD, standard deviation. Percentages are compared using the Fisher's exact test. Interval measures are summarized as medians (range) and compared using the exact Mann-Whitney test. Continuous measures are summarized as means ± standard deviation and compared using the exact Mann-Whitney test.

<sup>b</sup> Significant.

impaired they could not undergo pituitary and NB testing. These factors may have resulted in an underestimate of the true rate of hypopituitarism, particularly given that injury severity as measured by acute CT findings was predictive of chronic hypopituitarism.

**Time Course**

Regarding the timeline of development of post-TBI hypopituitarism, there have been case reports of spontaneous pituitary function recovery, including resolution of isolated GHD (6, 34, 46). As seen in this study, it appears that recovery can

**TABLE 7. Computed tomographic findings of growth hormone deficiency and growth hormone insufficiency versus growth hormone-sufficient patients 6 to 9 months after injury<sup>a</sup>**

Acute computed tomographic finding	GHD/GHI, n = 11 (15.7%)	GH-sufficient, n = 59 (84.3%)	P value
Midline shift >4 mm	2 (18%)	15 (25%)	1.000
Diffuse brain swelling	10 (91%)	31 (53%)	0.021 <sup>b</sup>
Hypothalamic swelling or hemorrhage	4 (36%)	11 (19%)	0.233
Effaced cisterns	6 (55%)	27 (46%)	0.745
SAH/suprasellar SAH	9 (82%)	33 (56%)	0.180
Evacuated subdural hemorrhage	1 (9%)	9 (15%)	1.000
Evacuated intracranial hemorrhage or contusion	4 (36%)	2 (3%)	0.005
Multiple contusions	7 (64%)	28 (47%)	0.513
Shearing injuries (deep punctuate hemorrhage)	4 (36%)	15 (25%)	0.474
Cranial or facial fracture	7 (64%)	24 (41%)	0.196
Median aggregate computed tomographic score (range)	5 (2–8)	3 (0–8)	0.019 <sup>b</sup>

<sup>a</sup> GHD, growth hormone deficiency; GHI, growth hormone insufficiency; GH, growth hormone; SAH, subarachnoid hemorrhage. Percentages are compared using the Fisher’s exact test. The interval measure is summarized as the median and compared using the exact Mann-Whitney test.

<sup>b</sup> Significant.

occur in up to 50% of patients with major deficits diagnosed at 3 months postinjury (6–8, 10). However, this study and others have shown that new deficiencies may develop more than 3 months postinjury. Aimaretti et al. (10) showed that four out of 51 (8%) patients tested at 3 months after injury had new hypopituitarism in at least one hormonal axis when retested 12 months after injury. Similarly, in the present study, 14% of patients showed new major hormonal deficits. The etiology of such deteriorating pituitary function is unclear, but it may be related to an ongoing involution or atrophy of the injured pituitary and infundibular structures. Given that we do not have hormonal testing data beyond the 6 to 9 month postinjury time point, it is uncertain whether further recovery or worsening of function will occur. Existing studies suggest, however, that most deficits diagnosed 6 to 9 months or more after injury are lasting.

**Risk Factors**

Although most previous studies have failed to show a definitive relationship between injury factors and the development of hypopituitarism, the current study and our original cohort study (51), suggest that the degree of brain injury on acute CT is the strongest predictor of subsequent dysfunction. All patients with major hormonal deficits in this series had severe brain injuries, including 87% with diffuse brain swelling. Previous studies that addressed this issue have had less detailed CT assessments or no imaging assessments (5, 7, 9, 10, 21, 58, 74). However, other studies have, on occasion, found new endocrinopathy after milder TBI (19, 21, 33, 51), suggesting that severe parenchymal brain injury, although commonly associated with new hypopituitarism, is not an essential condition for its development.

**Neurobehavioral and QOL Impact**

Regarding the impact of hypopituitarism on NB and QOL parameters, this study shows that patients with major hormonal deficits had greater disability by DRS compared with those without major deficits. Patients with isolated GHD or GHI also tended to demonstrate a greater rate of depression than those without GHD or GHI (90 versus 53%) and poor QOL in the SF-36 domains of fatigue and energy, emotional well being, and a trend toward worse general health. These findings are generally consistent with our recent report on a smaller cohort of patients with GHD or GHI (52) and suggest that disability, QOL, and depression are related to untreated hormonal deficiencies, particularly GHD and GHI. Although this link between hypopituitarism and poor outcome has been assumed, previous cohort studies have not included such NB and QOL analyses relative to hormonal status (5, 7, 9, 10, 21, 43, 58, 60, 74, 85).

Given that patients with major hormonal deficits had more severe brain injuries as seen on acute CT, differences in NB and QOL could be attributed to the brain injury per se and associated secondary insults. However, based on the known impact of untreated endocrinopathy on NB and QOL in general, it is likely that such deficits do hinder recovery after TBI. GHD and hypogonadism are particularly relevant, given that these deficits are the most common after TBI and have been associated with NB and QOL impairment that is qualitatively similar in many ways to that observed in TBI victims (3, 13, 18, 20, 30, 36, 39, 42, 45, 50, 54, 59, 71, 91). Both GHD and hypogonadism also lead to decreased lean body mass, poor exercise capacity, and increased fat mass that further contribute to poor QOL (18, 36, 41, 45, 80, 91). GH replacement improves NB function and QOL in patients with adult-onset

**TABLE 8.** Global and neurobehavioral outcome in growth hormone deficiency and growth hormone insufficiency versus growth hormone-sufficient patients at 6 to 9 months after injury<sup>a</sup>

Measure	GHD/GHI, n = 11 (16%)	GH-sufficient, n = 59 (84%)	P value
GOSE <sup>b</sup>	4.7 ± 1.1	5.6 ± 1.5	0.049 <sup>d,i</sup>
DRS <sup>c</sup>	4.6 ± 5.7	2.2 ± 2.5	0.068 <sup>e</sup>
<b>Memory</b>			
Buschke selective reminding, CLTR <sup>b</sup>	19.4 ± 12.1	24.6 ± 16.5	0.673
Rey complex figure <sup>b</sup>	13.7 ± 7.7	16.8 ± 8.3	0.287
Memory deficit present	8/10 (80%)	41/57 (72%)	0.717
<b>Concentration</b>			
Digit symbol, written <sup>b</sup>	35.6 ± 17.9	39.9 ± 15.1	0.112
Digit symbol, oral <sup>b</sup>	36.8 ± 12.3	47.7 ± 17.7	0.076
Concentration deficit present	8/11 (73%)	35/57 (61%)	0.734
<b>Depression</b>			
NB rating scale <sup>c</sup>	2.10 ± 0.57	1.69 ± 0.86	0.083 <sup>f</sup>
CES, depression <sup>c</sup>	16.0 ± 9.81	10.9 ± 10.9	0.100
Hospital anxiety, depression <sup>c</sup>	6.4 ± 4.2	3.5 ± 3.6	0.069
Depression deficit present	9/10 (90%)	31/59 (53%)	0.037 <sup>g,i</sup>
<b>Anxiety</b>			
Hospital anxiety <sup>c</sup>	3.6 ± 3.9	4.7 ± 3.9	0.404
Neurobehavioral rating scale, anxiety <sup>c</sup>	2.5 ± 2.4	1.7 ± 0.8	0.493
Anxiety deficit present	7/10 (70%)	32/59 (54%)	0.496
<b>Fatigue</b>			
NB rating scale, fatigue <sup>c</sup>	1.4 ± 0.5	1.3 ± 0.6	0.432
Fatigue deficit present	4/10 (40%)	14/58 (24%)	0.437
Total no. of NB deficits <sup>c</sup>	3.5 (2–5) (n = 10)	3 (0–5) (n = 59)	0.055 <sup>h</sup>

<sup>a</sup> GHD, growth hormone deficiency; GHI, growth hormone insufficiency; GH, growth hormone; GOSE, Glasgow Outcome Scale-Extended; NB, neurobehavioral; DRS, Disability Rating Scale; CLTR, consistent long-term retrieval; CES, Center for Epidemiological Studies. Percentages are compared using the Fisher's exact test. Interval measures are summarized as medians (range) and compared using the exact Mann-Whitney test. Continuous measures are summarized as means ± standard deviation and compared using the exact Mann-Whitney test.

<sup>b</sup> Greater scores represent better health.

<sup>c</sup> Lower scores represent better health. Multivariate *P* values were derived by controlling for best subset of predictors from age, Glasgow Coma Scale score, pupil status, hypotension, and computed tomography score.

<sup>d</sup> Multivariate *P* value of 0.12 controlling for Glasgow Coma Scale.

<sup>e</sup> Multivariate *P* value of 0.04 controlling for Glasgow Coma Scale.

<sup>f</sup> Multivariate *P* value of 0.07 controlling for computed tomographic score.

<sup>g</sup> Multivariate *P* value of 0.06 controlling for pupil status.

<sup>h</sup> Multivariate *P* value of 0.06 controlling for age and pupil status.

<sup>i</sup> Significant.

GHD (15, 17, 18, 20, 36, 39, 62, 72, 83, 84, 95). The benefits of testosterone for men and estradiol for women are also clear and are considered standard practice (13, 45, 50, 71, 91). Considering that there are no proven pharmacological therapies for chronically impaired TBI patients (1, 73), GH and gonadal steroid replacement in deficient patients may be beneficial, particularly for the pervasive problems of depression, emotional distress, and fatigue. Randomized trials of GH replacement therapy in TBI patients will hopefully definitively address this issue.

### Defining Hormonal Deficiency

In this study, we used standard pituitary hormonal testing, including stimulation testing for the corticotroph, somatotroph, and gonadotroph axes. (44). Although our definition of inadequate GH production was broader than the range of normal limits used in clinical settings, we justified using a less restrictive threshold of the 10th percentile value of a healthy control cohort to detect more subtle abnormalities of somatotroph function that might have clinical implications. An additional consideration is that the GHRH-arginine test may potentially result in

**TABLE 9. Quality of life in growth hormone deficiency and growth hormone insufficiency versus growth hormone-sufficient patients at 6 to 9 months after injury<sup>a</sup>**

Measure <sup>b</sup>	GHD/GHI, n = 11 (16%)	GH-sufficient, n = 59 (84%)	P value
QOL, AGHDA <sup>c</sup>	6.9 ± 6.2 (n = 9)	6.6 ± 6.6 (n = 57)	0.674
SF-36 <sup>d</sup>	n = 9	n = 57	
Physical functioning	70.0 ± 31.7	71.8 ± 30.2	0.726
Limitations due to physical health	38.9 ± 47.0	50.0 ± 42.5	0.542
Limitations due to emotional health	59.3 ± 49.4	81.3 ± 33.9	0.175
Energy and fatigue	48.3 ± 21.9	64.2 ± 24.0	0.053 <sup>e,h</sup>
Emotional well-being	60.9 ± 20.7	77.3 ± 22.4	0.018 <sup>f,h</sup>
Social functioning	66.7 ± 30.0	75.7 ± 26.9	0.319
Pain	65.0 ± 25.7	78.6 ± 22.5	0.129
General health	57.8 ± 18.7	75.3 ± 18.9	0.001 <sup>g,h</sup>

<sup>a</sup> GHD, growth hormone deficiency; GHI, growth hormone insufficiency; GH, growth hormone; QOL, quality of life; SF-36, Short Form-36; AGHDA, Assessment of Growth Hormone Deficiency in Adults.

<sup>b</sup> Continuous measures are summarized as means ± standard deviation and compared with the exact Mann-Whitney test.

<sup>c</sup> Lower scores represent better health.

<sup>d</sup> Greater scores represent better health. Multivariate P values derived by controlling for best subset of predictors from age, Glasgow Coma Scale, pupil status, hypotension, and computed tomography score.

<sup>e</sup> Multivariate P value of 0.03 controlling for computed tomography score.

<sup>f</sup> Multivariate P value of 0.02 controlling for computed tomography score.

<sup>g</sup> Multivariate P value of 0.07 controlling for hypotension.

<sup>h</sup> Significant.

**TABLE 10. Recent cohort studies of chronic posttraumatic hypopituitarism<sup>a</sup>**

Series (ref. no.)	No. of cases	Percentage with any deficiency (%)	Growth hormone (%)	Gonadal (%)	Adrenal (%)	Thyroid (%)	Diabetes insipidus (%)
Tanriverdi et al., 2006 (85)	52	51	38	8	19	6	NR
Herrmann et al., 2006 (43)	76	24	8	17	3	3	0
Leal-Cerro et al., 2005 (58)	99	42	10	29	11	10	1.7
Aimaretti et al., 2005 (10)	70	23	20	11	7	6	2.8
Agha et al., 2004, 2005 (5, 7)	102	28	10	12	13	1	6
Bondanelli et al., 2004 (21)	50	54	28	14	0	10	0
Lieberman et al., 2001 (60)	70	69	15	0	7	9	0
Kelly et al., 2000 (51)	22	36	18	23	0	4	0
Current series	70	21 (major) <sup>b</sup>	16	10.5	0	0	1.4
Total	611	37 (mean) <sup>c</sup>	16	14	8	5	2

<sup>a</sup> NR, not reported.

<sup>b</sup> Major, as defined in the “Materials and Methods” section as hormonal deficiency warranting replacement therapy.

<sup>c</sup> Mean deficiency rates are weighted means based on cohort size.

an underdiagnosis of hypothalamic-pituitary damage because use of GHRH allows potential hypothalamic dysfunction to be bypassed. In contrast, the insulin tolerance test, which is considered the “gold standard” for diagnosing GHD was not used because of the risk of hypoglycemic-induced seizures in patients who are at increased risk for seizures (12, 38).

Another important finding in this study was that the mean BMI was greater in the hormonally deficient patients than those

without a major hormonal deficiency, both at time of injury and at the time of stimulation testing. Greater BMI scores have been associated with a decreased degree of GH-responsiveness to both GHRH-arginine and the insulin tolerance test (76). Whether some of these more obese patients in this study had preexisting subclinical GHD or GHI is unclear. The finding of a higher pre- and postinjury BMI in the cohort of patients with any major chronic hormonal deficiency also raises the issue of

whether obesity itself is somehow a predisposing factor for the development of subsequent hypopituitarism.

## CONCLUSION

This analysis indicates that approximately 20% of patients develop major pituitary hormonal deficiencies, which are typically associated with relatively severe CT-defined brain injuries, 6 to 9 months after complicated mild, moderate, or severe TBI. In the chronic recovery phase, the presence of a major hormonal deficiency is associated with increased disability, whereas an insufficiency or deficiency of GH is associated with increased disability, poor QOL, and a greater likelihood of depression. The clinical significance of minor hormonal deficiencies that typically do not warrant hormone replacement therapy but which occur in almost 30% of long-term TBI survivors remains unclear and warrants further study. Given the high incidence of pituitary dysfunction after TBI, routine hormonal testing and appropriate hormone replacement therapy within 6 months of injury is recommended for all complicated mild, moderate, and severe TBI patients.

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## COMMENTS

This study is weakened by the relatively low follow-up rate. Another potentially confounding factor is the inclusion of patients with less severe injuries, who may be expected to have a lower rate of posttraumatic hypopituitarism. Also, many of the findings reported here overlap with those from previously reported studies. Despite these limitations, Bavisetty et al. were able to document a relationship between the extent of parenchymal injury demonstrated by computed tomography and subsequent pituitary dysfunction as well as an association between major hormonal dysfunction and increased disability. In particular, growth hormone (GH) deficiency or insufficiency is associated with a worse quality of life and greater likelihood of depression. Of interest is the fact that as many as half of major hormonal deficits present at 3 months after injury resolve within several months, and, on the other hand, new major hormonal deficits not seen at 3 months develop within a few months in up to 14% of patients. Thus, although hormonal screening results are reasonable early after injury, it may be wise to repeat such tests later during recovery to see whether patients have spontaneously recovered from their hormonal deficits or if they have developed new ones.

Alex B. Valadka  
Houston, Texas

The authors have produced this large study, which is probably the most important contribution to this field, using modern dynamic endocrine challenge testing techniques. It is important because it documents a knowledge gap in most neurosurgical and head injury texts.

Although the study cohort of 70 patients was degraded by major losses to follow-up, the implication is that even higher incidences of hormonal deficiency would be found. With the detailed testing methods used, 21% of patients had a major hormonal deficiency, and 29% had minor deficiencies. Almost half had both major and minor deficiencies, and the most common defect was in GH secretion, followed by gonadotrophin deficiencies. No patient had adrenal or thyroid deficiencies.

Many of these patients with severe pituitary insufficiency were not receiving replacement hormones, consistent with the uncertainty about GH replacement in general. As expected, the patients with the worst

injuries had major endocrine defects, and endocrine defects correlated with more depression, fatigue, and worse general health.

Most strikingly, 14% of the patients without hormonal deficiency at 3 months developed new deficits when retested at 6 to 9 months. It was uncertain whether pituitary involution is the cause, owing to changes in the body mass index of the patients, although the higher body mass seen in the GH-deficient patients argues against this theory.

It was also uncertain whether these changes represent hypothalamic or anterior pituitary degeneration. It would be important to consider magnetic resonance imaging volumetric studies of both the pituitary and the hypothalamus in this intensely studied group of patients to try to resolve this uncertainty for the future.

Clearly, in younger patients, with traumatic brain injury (TBI), GH and gonadotrophin endocrine testing should be considered, and gonadotrophic replacement should be given when deficiencies are found. For GH deficiency, however, the situation remains unclear. We look to the UCLA group to resolve this issue in the future, with clinical trials of replacement therapy in this cohort with severe TBI.

**M. Ross Bullock**  
*Miami, Florida*

**G**H deficiency has become more evident as a clinical entity in recent years with ever-increasing discussion about replacement therapy. Quality of life is always an important issue, but GH replacement may be advisable for metabolic issues. It has been known that TBI can cause pituitary dysfunction, but longer term follow-up of the hormonal status of patients with TBI has not been extensively reported. This article provides 6- to 9-month follow-up data showing both the ability for pituitary function to improve and also the fact that it will deteriorate in some patients. The advice that routine delayed hormonal testing should be done is very reasonable, given the 20% incidence of chronic need for hormonal replacement.

It is not surprising that the somatotroph and gonadotroph axes are the most vulnerable as that is also the case with adenomas. The association of GH deficiency/GH insensitivity with increased disability, depression, and poor quality of life needs further study as noted by the authors. Whether this is a cause and effect relationship in any way or just an association because of the extent of injury is not clear. It will also be interesting to see a well-designed study to evaluate the effects of replacement GH therapy on the quality of life in patients with TBI.

**Kalmon D. Post**  
*New York, New York*

**T**his work builds upon previous studies by a group of established investigators on the topic of chronic hypopituitarism after TBI. There have been many previous studies on this topic, and chronic pituitary dysfunction is increasingly recognized to affect patients with TBI. Patients with complicated mild, moderate, and severe TBI were prospectively enrolled and assessed at 3 and 6 to 9 months after injury for major and minor hormonal deficits as well as neurobehavioral deficits. The authors found that approximately 20% of the patients in the study developed major pituitary hormonal deficiencies and that these were typically correlated with severity of computed tomographic findings. In addition, the presence of a major hormonal deficiency is associated with increased disability, whereas an insufficiency or deficiency of GH is associated with increased disability, poor quality-of-life, and a higher likelihood of depression. Unfortunately, a significant number of patients were lost to follow-up, despite considerable effort on the part of the investigating team. Nevertheless, the study does identify the fact that computed tomographic findings are predictive of chronic hypopituitarism. In addition, the study highlights the important relationship between hypopituitarism and neurobehavioral and quality of life measures. Importantly, this study suggests that routine hormonal testing and appropriate replacement therapy should be done for all patients who have complicated mild, moderate, and severe TBI.

**Charles Y. Liu**  
*Los Angeles, California*

**T**he authors performed a prospective analysis of 70 patients with traumatic brain injury (TBI) and concluded that nearly half the patients had some sort of pituitary disorder (a much higher incidence than the general population) and that 20% warranted some form of hormone replacement. They also noted increased disability, depression, and poor quality of life in patients suffering from GH abnormalities. They conclude that since untreated pituitary deficiencies may lead to significant negative impact on physical and mental health, TBI patients should be screened for these deficiencies and treated accordingly.

This is a carefully conducted prospective analysis that makes some very important observations. Endocrine dysfunction is relatively common after TBI, can occur in a delayed fashion after injury, and occasionally resolves spontaneously. It is important that TBI patients be assessed and closely followed for endocrine disorders after TBI.

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