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Neurobehavioral and Quality of Life Changes Associated with Growth Hormone Insufficiency after Complicated Mild, Moderate, or Severe Traumatic Brain Injury

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ABSTRACT

Adult-onset growth hormone deficiency (GHD) has been associated with reduced quality of life (QOL) and neurobehavioral (NB) deficits. This prospective study tested the hypothesis that traumatic brain injury (TBI) patients with GHD or GH insufficiency (GHI) would exhibit greater NB/QOL impairment than patients without GHD/GHI. Complicated mild, moderate, and severe adult TBI patients (GCS score 3–14) had pituitary function and NB/QOL testing performed 6–9 months postinjury. GH-secretory capacity was assessed with a GHRH-arginine stimulation test and GHD and GHI were defined as peak GH <6 or ≤12 ng/mL (5th and 10th percentiles of healthy control subjects, respectively). Of 44 patients (mean age, 32 ± 18 years; median GCS, 7), one (2%) was GHD, seven (16%) were GHI, and 36 (82%) were GH-sufficient at 6–9 months post-injury. Mean peak GH was 8.2 ± 2.1 ng/mL in the GHD/GHI group versus 45.7 ± 29 ng/mL in the GH-sufficient group. The two groups were well-matched in injury characteristics, except that one patient with GHD had central hypogonadism treated with testosterone prior to NB/QOL testing. At 6–9 months postinjury, patients with GHD/GHI had higher rates of at least one marker of depression ($p < 0.01$), and reduced QOL (by SF-36 Health Survey) in the domains of limitations due to physical health ($p = 0.02$), energy and fatigue ($p = 0.05$), emotional well-being ($p = 0.02$), pain ($p = 0.01$), and general health ($p = 0.05$). Chronic GHI develops in approximately 18% of patients with complicated mild, moderate, or severe TBI, and is associated with depression and diminished QOL. The impact of GH replacement therapy on NB function and QOL in these TBI patients is being tested in a randomized placebo-controlled trial.

Key words: growth hormone deficiency; hypopituitarism; insulin-like growth factor–1; neurobehavioral; pituitary failure; quality of life; traumatic brain injury

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INTRODUCTION

DESPITE INCREASINGLY EFFECTIVE efforts in prevention, traumatic brain injury (TBI) remains a leading cause of mortality and morbidity around the world. In the United States, TBI is still the leading cause of disability among children and young adults (NIH, 1999; Adekoya et al., 2002). Each year approximately 500,000 persons sustain TBI in the United States, and a substantial proportion of the survivors have residual neurobehavioral (NB) sequelae such as memory and concentration deficits, depression, fatigue, and anxiety (NIH, 1999; Hellawell et al., 1999; Kraus and McArthur, 1996; Levin et al., 1990; Narayan et al., 2002). Although it has been suggested in recent cohort studies and reviews that post-TBI neurocognitive and quality of life (QOL) sequelae may, in part, be related to untreated neuroendocrine dysfunction, this possibility remains under-studied and unresolved (Agha et al., 2004; Aimaretti et al., 2004; Casanueva et al., 2004; Ghigo et al., 2005; Kelly et al., 2000; Lieberman et al., 2001; Popovic et al., 2004; Schneider et al., 2005; Urban et al., 2005). Because the pituitary gland is confined within the sella turcica by the diaphargma sella but tethered to the hypothalamus by the infundibulum, the hypothalamic-pituitary axis is susceptible to both mechanical and vascular insults (Ceballos, 1966; Daniel, 1963; Daniel et al., 1959; Kornblum and Fisher, 1969). Further injury to these neuroendocrine structures may result from secondary insults such as hypotension, hypoxia, severe anemia, and brain swelling (Chesnut et al., 1993a; Kelly et al., 2000). A number of cohort studies published since 2000 have documented that long-term pituitary dysfunction following moderate or severe TBI occurs in 25–40% of patients (Agha et al., 2004, 2005b; Aimaretti et al., 2004, 2005; Bondanelli et al., 2004; Kelly et al., 2000; Leal-Cerro et al., 2005; Lieberman et al., 2001; Popovic et al., 2004). The somatotroph axis appears to be the most vulnerable, with estimates of growth hormone (GH) deficiency (GHD) of 6–25% in tested TBI patients. In contrast, thyrotroph and corticotroph deficiency are relatively uncommon, with rates averaging 4–6%, while the gonadotroph axis appears to have intermediate rates of dysfunction, averaging 8–12% (Agha et al., 2004, 2005b; Aimaretti et al., 2004, 2005; Bondanelli et al., 2004; Kelly et al., 2000; Leal-Cerro et al., 2005; Lieberman et al., 2001; Popovic et al., 2004).

GHD may be particularly relevant to the chronic recovery phase after TBI given that (1) it has been associated with NB impairment and reduced QOL, which is qualitatively similar in many aspects to that observed in TBI victims (Abs et al., 2005; Bengtsson et al., 1993; Blum et al., 2003; Deijen et al., 1996; Feldt-Rasmussen et al., 2004; Giusti et al., 1998; Hellawell et al., 1999; Koltowska-Haggstrom et al., 2005; Levin et al., 1990); (2) it has been associated with somatic derangements, including decreased lean body mass, poor exercise capacity, diminished bone mineral density, and increased fat mass, which may also contribute to poor QOL after TBI (Bengtsson et al., 1993; Feldt-Rasmussen et al., 2004; Gotherstrom et al., 2001; Rosen et al., 1997); and (3) GH replacement therapy reportedly improves NB function and QOL in patients with adult-onset GHD (Arwert et al., 2005a,c; Bengtsson et al., 1993; Blum et al., 2003; Feldt-Rasmussen et al., 2004; Giusti et al., 1998; Mahajan et al., 2004; Mukherjee et al., 2005; Soares et al., 1999; Svensson et al., 2004; Wiren et al., 1998).

We thus hypothesized that (1) GHD, either as a primary factor or acting in a synergistic manner with the residual effects of brain injury, could limit maximal recovery after TBI; and (2) patients with chronic GHD would have worse NB deficits and a reduced QOL compared to those without GHD. To test these hypotheses, patients in the chronic phase after moderate or severe TBI underwent anterior and posterior pituitary function testing, including a GH-releasing hormone (GHRH)–arginine stimulation test to assess GH-secretory capacity (Aimaretti et al., 2001; Ghigo et al., 2001; Qu et al., 2005). Using the criteria described below, patients with GHD were compared to those with normal GH-secretory capacity using NB and QOL outcome measures. Given that the definition and absolute threshold for adult-onset GHD continues to be somewhat controversial (Aimaretti et al., 1998), we chose to define GH-secretory capacity at two cut-points of GHD and GH insufficiency (GHI), which correspond to the 5th and 10th percentile levels of peak GH in response to the GHRH-arginine stimulation test in a healthy control cohort.

METHODS

Approval

The Institutional Review Boards of each participating medical center approved this study. In the acute injury phase, informed proxy consent was obtained within 48 h of admission to Harbor–UCLA or UCLA Medical Centers, and within 24 h of admission to UC Davis Medical Center. Patients provided consent for study participation in the chronic phase (3–9 months after TBI) prior to pituitary stimulation testing and NB/QOL testing.

Enrollment Criteria and Initial Traumatic Brain Injury Management

Enrollment criteria for this prospective study included (1) age 14–80 years and admitted to the intensive care unit (ICU) of one of three Level 1 trauma centers within 24 h of injury, (2) an initial head computed tomography

(CT) showing acute intracranial hemorrhage, (3) a post-resuscitation Glasgow Coma Scale (GCS) score of 3–14 or a deterioration to a GCS of ≤14 within 24 h of admission. Patients were further categorized as sustaining a complicated mild TBI (GCS 13–14), moderate TBI (GCS 9–12), or severe TBI (3–8) (Borgaro et al., 2003; Teasdale and Jennett, 1974), and (4) recovery at 6–9 months post-injury to a Glasgow Outcome Scale–Extended (GOS-E) category of lower or better severe disability and able to participate in NB testing. Patients were excluded if they were pregnant, or had cancer, AIDS, severe neurological or psychiatric illness, pre-existing adrenal or pituitary insufficiency, or had received glucocorticoids within 3 months of injury.

All patients were admitted to the ICU after initial stabilization or after craniotomy for intracranial hematoma evacuation. Patient management was in accordance with the *Guidelines for the Management of Severe Head Injury* (Bullock et al., 1996), including an algorithm for maintaining intracranial pressure (ICP) at <20 mm Hg and cerebral perfusion pressure (CPP) above 60–70 mm Hg.

Acute Hormonal Testing

As recently described, all patients had serial adrenocorticotrophic hormone (ACTH) and cortisol blood draws at 6 a.m. and 4 p.m. while in the ICU (Cohan et al., 2005). Adrenal insufficiency was defined as two consecutive cortisol values of ≤15 μg/dL or one cortisol level of <5 μg/dL. In the majority of patients, daily 6 a.m. serum samples for insulin-like growth factor–1 (IGF-1) were also obtained. Urine specific gravity was recorded on a daily basis.

Pituitary Stimulation Testing

At 3 months and again at 6 months post-injury, patients were scheduled for dynamic anterior pituitary function testing in the General Clinical Research Center of their respective hospitals between 8 a.m. and 12 noon after an overnight fast. However, complete pituitary stimulation and NB/QOL testing were deferred up to 9 months post-injury in some patients due to logistical problems. Patients diagnosed with adrenal insufficiency, hypothyroidism, or hypogonadism at the initial stimulation testing were placed on appropriate hormone replacement therapy, and therapeutic replacement was confirmed in any of these deficient axes prior to undergoing NB/QOL testing. In this way, when NB/QOL testing was performed at the 6–9-month post-injury time point, the only possible untreated hormonal deficiency present was for GH.

The following tests were performed after baseline blood draws at −30 min and time zero: (1) GHRH-arginine stimulation test to assess somatotroph function (Aimaretti et al., 1998, 2001; Ghigo et al., 2001); (2) low-dose cortrosyn stimulation test to assess corticotroph function (Abdu et al., 1999; Zarkovic et al., 1999); (3) gonadotropin-releasing hormone (GnRH) stimulation test to assess gonadotroph function, by measuring both leutinizing hormone (LH) and follicle-stimulating hormone (FSH); (4) measurement of free T4, total T4, and thyroid-stimulating hormone (TSH) for thyrotroph function; and (5) measuring of prolactin to assess lactatroph function. Immediately after a time zero blood draw, a 30-min arginine infusion (30 g over 30 min) was started, and injections of GHRH (1 μg/kg), cortrosyn 1 μg, and GnRH 100 μg IV were given. Blood draws were then performed at 15, 20, 30, 60, 90, and 120 min for the various anterior pituitary hormones and their target hormones. Posterior pituitary function was assessed by obtaining urine sodium, osmolality and specific gravity within the hour prior to time zero and serum sodium, BUN, creatinine, osmolality, and arginine vasopressin (AVP) at time zero.

Hormone Analysis

Serum samples for all hormones, including GH, were stored at −20°C before assay by the GCRC Core Laboratory of the Harbor–UCLA Medical Center. GH was measured by an enzymatically amplified "two-step" sandwich-type immunoassay with reagents obtained from DSL (DSL-10-1900 hGH ELISA; Webster, TX) and validated at the Core Laboratory of the Harbor–UCLA Medical Center GCRC. The lower limit of quantitation is 0.1 μg/L. The intra-assay and inter-assay coefficients of variation are less than 8% and 14%, respectively. The recovery of GH from serum spiked with 0.1–15 μg/L of GH was 92–112%.

Healthy Control Cohort and Definition of Growth Hormone Deficiency

Healthy subjects were recruited by advertisements posted at Harbor–UCLA and UCLA Medical Centers. Those with previous diagnoses of endocrine diseases, currently on hormone replacement therapy, and pregnant females or those on birth control pills for the past 3 months were excluded. Although not studied at the same phase of the menstrual cycle, all women reported a history of regular menses. All male subjects had normal serum total testosterone concentrations. Healthy subjects who had GHRH-arginine testing consisted of 41 volunteers (19 males, 22 females), aged 20–50 years, with Body Mass Index (BMI) of 16–32.5; GHD and GHI were defined as a peak GH of <6 ng/mL (below 5th percentile) and <12.1 ng/mL (below 10th percentile), respectively (Qu et al., 2005). From our study, peak GH response to GHRH-argi-

nine had a significant negative correlation with BMI, and gender differences in peak GH response became insignificant when BMI was taken into consideration.

Neurobehavioral and Quality of Life Testing

As detailed in Table 1, all patients underwent NB/QOL testing at 6–9 months post-injury and within 2 weeks of undergoing pituitary stimulation testing. The NB testing battery assessed the five domains of memory, concentration, depression, anxiety, and fatigue (Buschke and Fuld, 1974; McCauley et al., 2001a,b; Radloff, 1977; Rey, 1941; Smith, 1973). These specific domains were selected because prior studies indicate such deficits often persist following TBI as well as in patients with adult-onset GHD (Arwert et al., 2005a,b,c; Deijen et al., 1996, 1998; Hellawell et al., 1999; Levin et al., 1990; Rollero et al., 1998; van Dam et al., 2000). 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, the patient was classified as having depression. From these scores, a total number of NB deficits, ranging from 0 to 5, was calculated as an index of total impairment, with one point given for any abnormal test in each of the five NB domains.

Two QOL measures were also performed including the Quality of Life–Assessment of GH Deficiency in Adults (QOL-AGHDA), which uses a 20-point scale, and the SF-36 Health Survey, which tests eight "health concepts" and has a 0–100-point scale (Blum et al., 2003; Findler et al., 2001; Koltowska-Haggstrom et al., 2005; MacKenzie et al., 2002; McGauley et al., 1990; McKenna et al., 1999; Ware and Sherbourne, 1992). Additional global outcome measures included the eight-point GOS-E and the Disability Rating Scale (DRS), which uses a 30-point scale (Teasdale et al., 1998; Wagner et al., 2002; Wilson et al., 1998, 2000).

Testing was performed in a quiet setting over a 2–3-h period at one of the participating medical centers. The neuropsychologist performing the tests had no knowledge of the subjects' hormonal status. If stimulation testing documented deficiencies of thyroid, cortisol, testosterone (men), or estrogen (women), NB/QOL testing was repeated after hormone replacement therapy had been in-

Table 1. Neurobehavioral and Quality of Life Testing Battery

Neurobehavioral domain	*Test used*	*Criteria for impairment*
Global outcome measures		
Glasgow Outcome Scale–Extended		
Disability Rating Scale		
Memory impairment	Buschke Selective Reminding Test	
	Continuous Long-Term Retrieval (CLTR)	Score <1
	Rey Complex Figure	Score <7
Concentration/attention deficits	Digit Symbol Modalities–written	Score <40
	Digit Symbol Modalities–oral	Score <50
Depression	Neurobehavioral Rating Scale	Depression score >1
	CES–Depression Scale	Score >16
	Hospital Anxiety–Depression Scale	Score >7
Anxiety	Hospital Anxiety–Depression Scale	Anxiety score >12
Fatigue	Neurobehavioral Rating Scale	Fatigue score >1
Aggregate Neurobehavioral Score	One point each for impairment in memory, concentration, depression, anxiety or fatigue (range 0–5)	
Quality of life measures	Physical functioning	
SF-36	Limitations due to physical health	
	Limitations due to emotional health	
	Energy and fatigue	
	Emotional well-being	
	Social functioning	
	Pain	
	General health	
Quality of Life–Assessment of GHD in Adults		

CES, Center for Epidemiological Studies; GHD, growth hormone deficiency.

stituted with documented normal hormonal levels of all axes, with the exception of GH replacement therapy.

Injury Characteristics Potentially Associated with Growth Hormone Deficiency or Insufficiency

Clinical parameters. Age, post-resuscitative GCS score, post-resuscitative pupillary status (both normal, one abnormal, both abnormal), Injury Severity Score (ISS), length of ICU stay, and 6-month GOS-E score were recorded for each subject (Jennett and Bond, 1975).

Ischemia factors. Factors associated with possible ischemic insult to the hypothalamic-pituitary axis included hypotension (systolic blood pressure <90 mm Hg) or severe anemia (hematocrit <25%) during the patients' ICU stay or hypoxia (PaO_2 <60 mm Hg, S_aO2 <90%, within 24 h of injury, or agonal respirations or apnea in the field (Ariza et al., 2004; Chesnut et al., 1993b; Jiang et al., 2002; Marmarou et al., 1991; Miller et al., 1978). As described in our recent report on acute adrenal insufficiency after TBI, an ischemia score ranging from 0 to 3 was also calculated for each subject, with 1 point each for hypotension, hypoxia or severe anemia (Cohan et al., 2005).

Computed tomography findings. The following findings of intracranial injury, all of which have been associated with worse long-term outcome after TBI, were recorded from patients' first and second CT scans obtained within 24 h of injury: basilar cistern compression, diffuse brain swelling, evacuated acute subdural hematoma (SDH), evacuated intracerebral hematoma (ICH), multiple contusions, subarachnoid hemorrhage, hypothalamic hemorrhagic or swelling, diffuse punctuate (subcortical) hemorrhage (consistent with shearing injuries), and skull/facial fractures (calvarial, skull base, sphenoid, or facial) (Eisenberg et al., 1990; Glenn et al., 2003; Kraus et al., 2003; Tomei et al., 1991). An aggregate CT score from 0 to 10 was calculated for each patient, with one point added for each of the above CT findings.

Intracranial pressure, CPP, and blood pressure. For patients in whom an ICP monitor was placed, mean and maximal ICP and CPP, total hours where ICP was >20 mm Hg, and total hours where CPP was <50 mm Hg were recorded (Jiang et al., 2002; Marmarou et al., 1991; Marshall et al., 1991a,b; Sarrafzadeh et al., 2001). Hourly mean arterial pressure (MAP) was also recorded.

Acute adrenal insufficiency and diabetes insipidus status. Patients were categorized as to whether or not they developed acute adrenal insufficiency (AI) as recently defined based on serial serum cortisol blood draws (Cohan et al., 2005). Patients were defined as having AI if two consecutive cortisol levels were ≤15 μg/dL or one cortisol level was <5 μg/dL. Subjects were categorized as having acute diabetes insipidus if they had a urine specific gravity of ≤1.005 with a urine output of greater than 300 mL/h for 2 h or more, and required treatment with desmopressin acetate (DDAVP).

Body Mass Index calculations. BMI was calculated acutely after injury based on patients' height and weight taken within 24 h of injury. The BMI was recalculated at the time of stimulation testing 6–9 months post-injury. Changes in BMI acutely and at 6–9 months were compared between GHD/GHI patients and those with GH sufficiency.

Statistical Analysis

For purposes of this report, given the relatively small number of patients, those with GHD and GHI were grouped together, so that all comparisons presented are between the group of eight patients whose peak GH values were below the 10th percentile (<12.1 ng/mL) and the 36 patients whose values were above the 10th percentile. Data with approximately normal distributions are summarized with mean ± SD. Data with skewed distri-

TABLE 2. HORMONAL RESULTS AND BMI CHANGES IN GHD/GHI VERSUS GH-SUFFICIENT PATIENTS

Test[a]	*GHD/GHI,* n = *8 (18%)*	*GH-sufficient,* n = *36 (82%)*	p-*value*
Peak GH after GHRH-arginine	8.2 ± 2.1	45.7 ± 29.0	n/a
Baseline IGF-1 at stimulation testing	206 ± 69	262 ± 93	0.20
BMI at time of injury	28.7 ± 2.7	25.1 ± 4.7	0.01
BMI at time of stimulation testing	27.6 ± 2.3	24.6 ± 2.5	0.01

[a]Measures are summarized as mean ± SD, standard deviation, and compared using the Yuen-Welch robust test.

BMI, Body Mass Index; GH, growth hormone; GHD, GH deficiency; GHI, GH insufficiency; GHRH, GH-releasing hormone; IGF-1, insulin-like growth factor–1.

butions (age, GCS, ISS, CT score, durations of ICU and hospitalization, and total number of NB deficits) are summarized with percentiles. Comparisons between the two groups (GHD/GHI vs. non-GHD) were performed with *t*-tests for normally distributed data, Mann-Whitney tests for skewed data, Fisher's exact tests for percentages, and the Yuen-Welch robust test for group differences in means trimmed by 20% (Yuen, 1974) using R version 2.1.1. Robust analyses are appropriate for small sample sizes with unequal variances, as single outliers can exert substantial and potentially misleading leverage on statistical estimates (Keselman et al., 2004; Wilcox, 1997).

RESULTS

Patient Enrollment and Study Attrition

Between June 2002 and September 2004, 129 patients were enrolled into the acute phase (immediately after head injury) of our hypopituitarism after TBI study. A total of 33 patients died during this phase; an additional six received steroids acutely and were dropped from further study. A total of 13 were lost to follow-up before the 6-month contact. Re-consenting of participants could not be completed for 23 persons. Eight patients either did not appear for their appointed re-contact or remained too neurologically impaired to participate further; two did not provide complete testing. The final number of subjects included in the following analyses was 44.

Rate of Growth Hormone Deficiency and Insufficiency and Body Mass Index Changes

Pituitary stimulation testing with GHRH-arginine performed at 6–9 months post-injury (median, 7 months) identified one patient (2%) with GHD, seven patients (16%) with GHI, and 36 patients (82%) with GH sufficiency, for a total rate of GHD/GHI of 18%. One patient

Table 3. Individual Injury Characteristics of Patients with GHD/GHI[a]

Patient age/sex	*GCS*	*ISS*	*Mechanism*	*Hypotension/ hypoxia*	*Lowest Hct*	*Abnormal pupils*	*Hours ICP > 20*	*CT findings*	*GOS-E*
21 F	7	30	Fall	Yes/no	27	2	27	MLS, DS, AC, SDH, MC, HYS, FX	4
21 M	3	48	Peds-auto	Yes/yes	22	2	24	DS, SI	5
24 M	8	16	Fall	No/no	34	0	N.D.	MC, SAH, FX	6
28 M	10	25	GSW	No/no	26	0	11	MLS, DS, AC, ICH, SAH, FX	5
32 M	3	38	MCA	Yes/yes	30	2	33	DS, SAH, SI, FX	3
42 M	15[b]	25	Fall	No/no	33	0	N.D.	DS, MC, SAH, SI FX	7
58 M	7	9	Fall	No/no	35	0	0	DS, MC, SAH	5
62 M	11	25	Peds-auto	Yes/no	32	0	47	DS, AC, ICH, MC, SAH, HYS, SI, FX	4

[a]GCS, post-resuscitation Glasgow Coma Scale score. Mechanism: peds-auto, pedestrian vs. auto; GSW, gunshot wound; MCA, motorcycle accident. Hours ICP >20 mm Hg: N.D., no ICP monitoring performed. CT findings, MLS–midline shift >4 mm; DS, diffuse swelling; AC, abnormal cisterns; SDH, evacuated subdural hematoma; ICH, evacuated intracerebral hematoma; MC, multiple contusions; SAH, subarachoid hemorrhage; HYS, hypothalamic swelling or hemorrhage; SI, shearing injuries (diffuse subcortical punctuate hemorrhage); FX, calvarial or facial fractures. GOS-E, extended Glasgow Outcome Scale score: 7, lower good recovery; 6, upper moderate disability; 5, lower moderate disability; 4, upper severe disability; 3, lower severe disability.

[b]Patient deteriorated to GCS <15 within 24 h of admission.

GH, growth hormone; GHD, GH deficiency; GHI, GH insufficiency; ISS, Injury Severity Score; Hct, hematocrit; ICP, intracranial pressure; CT, computed tomography.

with GHD also had central hypogonadism and was placed on testosterone replacement with normalization of his total and free testosterone level prior to repeat stimulation testing and NB/QOL testing.

As seen in Table 2, grouping the GHD and GHI patients together, the peak GH after GHRH-arginine was 8.2 ± 2.1 ng/mL in the GHD/GHI group versus 45.7 ± 29.0 ng/mL in the GH-sufficient group. The mean acute post-injury BMI was higher in patients with GHD/GHI compared to that for GH-sufficient patients (28.7 ± 2.7 vs. 25.1 ± 4.7, respectively; $p < 0.01$) and remained higher at the time of stimulation testing 6–9 months post-injury ($p < 0.01$).

Injury Characteristics

As shown in Table 3, the eight patients with GHD/GHI sustained relatively extensive brain injuries, often complicated by hypotension, hypoxia, and/or raised ICP; all eight patients had multiple CT findings, including seven (88%) with diffuse brain swelling. However, as shown in Table 4, the patients with GHD/GHI were similar to the GH-sufficient patients in age, ISS, GCS, pupillary changes, length of ICU and hospital stay, ischemia score, and ICP and CPP measures. The presence of acute adrenal insufficiency and diabetes insipidus were also similar between groups. Overall, CT scan findings were also similar in the two groups of TBI patients, apart from a trend for higher aggregate CT scores in patients with GHD/GHI ($p = 0.09$) (Table 5).

Neurobehavioral and Quality of Life Comparisons

As shown in Table 6, the GHD/GHI and GH-sufficient groups were similar in terms of GOS-E and DRS scores

Table 4. Acute Injury Characteristics of GHD/GHI versus GH-Sufficient Patients[a]

Characteristic	*GHD/GHI,* n = *8 (18%)*	*GH-sufficient,* n = *36 (82%)*	p-*value*
Mean age ± SD	36 ± 16	32 ± 18	0.52
[range]	[21–62]	[14–77]	
Male gender	7 (88%)	26 (72%)	0.66
Median post-resuscitation GCS (i.q.r.) [range]	7.5 (6–10)	7.5 (7–9)	1.00
	[3–15]	[3–15]	
Severe TBI (pre-resuscitation GCS ≤8)	5 (62.5%)	25 (69%)	1.00
Median ISS [range]	25 (23–32)	29 (25–42)	0.70
	[9–48]	[10–66]	
Abnormal pupils (one or both)	3 (37.5%)	13 (36%)	1.00
Hypotension	4 (50%)	19 (53%)	1.00
Hypoxia	2 (25%)	10 (28%)	1.00
Anemia	1 (13%)	6 (17%)	1.00
Median Ischemic Score[b] [range]	0.5 (0–1.25)	1.0 (0–1.25)	0.66
	[0–3]	[0–3]	
Acute ICP and CPP course[c]			
Mean ICP mm Hg ± SD	14 ± 3	14 ± 3	0.98
Hours ICP >20 mm Hg	24 ± 17	17 ± 15	0.40
Mean CPP mm Hg ± SD	78 ± 88	76 ± 9	0.52
Hours CPP <50 mm Hg	15 ± 25	6 ± 9	0.58
Acute hormonal changes			
Acute adrenal insufficiency	5 (62.5%)	19 (53%)	0.71
Acute diabetes insipidus	0	2 (5.6%)	1.00
Median days of ICU stay (i.q.r.)	12 (5.7–24.7)	10 (5.0–18.5)	0.77
[range]	[3–37]	[1–46]	
Median days of hospitalization (i.q.r.)	18 (7.75–29.5)	16 (9.0–29.5)	0.94
[range]	[3–42]	[3–49]	

[a]Percentages are compared using Fisher's exact test. Interval measures are summarized as medians [i.q.r.]: 25th percentile (75th percentile), and compared using the Mann-Whitney test. Continuous measures are summarized as means ± standard deviation (SD), and compared using the *t*-test.

[b]Ischemia Score is comprised of 1 point for each of hypotension, hypoxia, and anemia.

[c]ICP and CPP not assessed in two GHD/GHI cases and 19 GH-sufficient cases.

GH, growth hormone; GHD, GH deficiency; GHI, GH insufficiency; GCS, Glasgow Coma Scale; TBI, traumatic brain injury; ISS, Injury Severity Score; ICP, intracranial pressure; CPP, cerebral perfusion pressure; ICU, intensive care unit.

TABLE 5. ACUTE CT FINDINGS FOR GHD/GHI PATIENTS VERSUS GH-SUFFICIENT PATIENTS[a]

CT finding	*GHD/GHI,* n = *8 (18%)*	*GH-sufficient,* n = *36 (82%)*	p-*value*
Midline shift >4 mm	2 (25%)	8 (40%)	1.00
Diffuse brain swelling	7 (88%)	21 (58%)	0.22
Hypothalamic swelling or hemorrhage	2 (25%)	6 (17%)	0.62
Effaced cisterns	3 (38%)	16 (44%)	1.00
Subarachnoid hemorrhage	6 (75%)	16 (44%)	0.24
Evacuated SDH	1 (12.5%)	7 (19%)	1.00
Evacuated ICH or contusion	2 (25%)	1 (3%)	0.08
Multiple contusions	5 (62.5%)	16 (44%)	0.45
Shearing injuries (deep punctuate hemorrhage)	4 (50%)	10 (28%)	0.40
Cranial or facial fracture	6 (75%)	17 (47%)	0.25
Median aggregate CT score (i.q.r.) [range]	4.5 (3.0–6.5) [2–8]	3 (2.0–5.0) [0–8]	0.09

[a]Percentages are compared using Fisher's exact test. Interval measure is summarized as median (interquartile range [i.q.r.]: 25th percentile to 75th percentile), and compared using the Mann-Whitney test.

CT, computed tomography; GH, growth hormone; GHD, GH deficiency; GHI, GH insufficiency; SDH, subdural hematoma; ICH, intracerebral hematoma.

recorded at 6-months post-injury or later. However, in comparison to the GH-sufficient group, the GHD/GHI cohort had higher rates of at least one indicator of depression (100% versus 47%; $p < 0.01$) and a trend of a higher number of total NB deficits that included the five domains of memory, concentration, depression, anxiety, and fatigue ($p = 0.07$). As seen in Table 7, QOL was worse in the GHD/GHI group compared to the GH-sufficient group in multiple domains as measured by the SF-36, including limitations due to physical health ($p = 0.02$), energy and fatigue ($p = 0.05$), emotional well-being ($p = 0.02$), pain ($p = 0.01$), and general health ($p = 0.05$). However, the QOL-AGHDA was similar between the two groups.

DISCUSSION

In this cohort of 44 moderate and severe TBI patients, eight patients or 18% of the total cohort met the criteria for GHD/GHI at 6–9 months post-injury. Acutely, the GHD/GHI patients were similar in overall injury characteristics to the 36 GH-sufficient patients, although there was a weak trend of a higher aggregate CT score, suggesting a greater degree of overall parenchymal brain injury in the patients with GHD/GHI. At 6–9 months post-injury, the GHD/GHI group exhibited higher rates of depression and a lower QOL in the domains of physical health, energy, pain, emotional well-being, and general health.

Defining Growth Hormone Deficiency

The diagnosis of GH deficiency is established by documenting a low age-adjusted IGF-1 level or by a provocative stimulation test, typically with the insulin tolerance test or the GHRH-arginine assessment used in this study (Aimaretti et al., 1998; Gharib et al., 2003). The importance of using a stimulation test for diagnosing GHD is emphasized by the fact that, in approximately one-third of such patients, the age-adjusted IGF-1 level is normal, and the diagnosis is only confirmed by stimulation testing (Hoffman et al., 1994). Although our definition of inadequate GH production was more relaxed 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 implications for outcome and clinical management. An additional consideration is that the GHRH-arginine test may potentially result in an under-diagnosis of hypothalamic-pituitary damage, because administration of GHRH allows potential hypothalamic dysfunction to be bypassed. In contrast, the insulin tolerance test, which is often considered to be the "gold standard" for diagnosing GHD, was not used in this study given the risk of hypoglycemic-induced seizures in TBI patients who were already at risk for post-traumatic epilepsy (Aimaretti et al., 1998; Ghigo et al., 2001). An additional consideration is that the mean BMI was higher in the GHD/GHI patients than the GH-sufficient pa-

TABLE 6. GLOBAL OUTCOME AND NEUROBEHAVIORAL OUTCOME[a]

Measure	*GHD/GHI,* n = *8*	*GH-sufficient,* n = *36*	p-*value*
GOSE[b]	4.9 ± 1.2	5.5 ± 1.4	0.80
DRS[c]	2.5 ± 1.3	2.0 ± 2.1	0.11
Memory			
Buschke Selective Reminding–CLTR[b]	24.6 ± 11.7	26.1 ± 16.9	0.82
Score ± 31	5/8 (63%)	23/34 (68%)	1.00
Rey Complex Figure[b]	12.1 ± 7.6	16.9 ± 8.8	0.12
Score <7	2/8 (25%)	6/36 (17%)	0.62
Memory deficit present	5/8 (63%)	23/36 (64%)	1.00
Concentration			
Digit Symbol–Written[b]	36.6 ± 19.4	41.4 ± 16.1	0.13
Score <40	6/8 (75%)	17/36 (47%)	0.25
Digit Symbol–Oral[b]	37.7 ± 13.2	50.3 ± 19	0.09
Score <50	5/7 (71%)	15/36 (42%)	0.68
Concentration deficit present	6/8 (75%)	19/36 (53%)	0.43
Depression			
Neurobehavioral Rating Scale[c]	2.1 ± 0.6	1.7 ± 0.9	0.02
Score >1	7/8 (88%)	17/36 (47%)	0.05
CES–Depression[c]	19.9 ± 10.4	9.4 ± 10.6	0.04
Score >16	5/7 (71%)	7/36 (19%)	0.01
Hospital Anxiety–Depression[c]	6.9 ± 4.2	3.2 ± 3.9	0.05
Score >7	3/7 (43%)	7/36 (19%)	0.32
Depression deficit present	8/8 (100%)	17/36 (47%)	0.01
Anxiety			
Hospital Anxiety[c]	5.1 ± 3.8	4.5 ± 3.9	0.84
Score >12	0/7 (0%)	0/36 (0%)	—
Neurobehavioral Rating Scale–Anxiety[c]	2.7 ± 2.6	1.8 ± 0.8	0.42
Score >1	6/8 (75%)	20/36 (56%)	0.44
Anxiety Deficit present	6/8 (75%)	20/36 (56%)	0.44
Fatigue			
Neurobehavioral Rating Scale–Fatigue[c]	1.4 ± 0.5	1.3 ± 0.5	0.50
Fatigue deficit present	3/8 (38%)	10/36 (28%)	0.68
Total number of neurobehavioral deficits[c]	3.5 (2.7–5)	2 (1.7–4)	0.07

[a]Percentages are compared using Fisher's exact test. Interval measures are summarized as medians (interquartile range [i.q.r.]: 25th percentile to 75th percentile), and compared using the Mann-Whitney test. Continuous measures are summarized as mean ± standard deviation (SD), and compared using the Yuen-Welch robust test.

[b]Higher scores represent better health.

[c]Lower scores represent better health.

GH, growth hormone; GHD, GH deficiency; GHI, GH insufficiency; GOSE, extended Glasgow Outcome Scale score; DRS, Disability Rating Scale; CLTR, Continuous Long-Term Retrieval; CES, Center for Epidemiological Studies.

tients, both at time of injury and at the time of stimulation testing. We (Qu et al, 2005) and others (Biller et al., 2002) have previously demonstrated a negative correlation between BMI and GH response to provocative stimuli. However, the influence of BMI and other factors on GH response remains an area of active investigation, and current clinical guidelines for defining and treating GHD are independent of BMI (Gharib et al., 2003).

Frequency of Growth Hormone Deficiency/Insufficiency after Traumatic Brain Injury

Prior cohort studies, including our own, indicate that the somatotrophs are particularly vulnerable to the primary and secondary injuries associated with moderate and severe TBI, with rates of post-TBI GHD of 6–25% in patients studied at least 3 months or more after injury

TABLE 7. QUALITY OF LIFE OUTCOMES

Measure[a]	*GHD/GHI,* n = *8*	*GH-sufficient,* n = *36*	p-*value*
QOL-AGHDA[b]	9.4 ± 8.2	5.9 ± 6	0.39
SF-36[c]			
Physical functioning	63.6 ± 33.5	72.1 ± 29.2	0.51
Limitations due to physical health	21.4 ± 36.6	47.2 ± 44.2	0.02
Limitations due to emotional health	47.6 ± 50.4	83.3 ± 30.3	0.15
Energy and fatigue	47.7 ± 22.5	63.7 ± 24.6	0.05
Emotional well-being	57.7 ± 20.8	77.4 ± 23.8	0.02
Social functioning	60.7 ± 31.0	76.4 ± 27.0	0.20
Pain	55.0 ± 18.9	76.2 ± 23.9	0.01
General health	57.9 ± 19.1	76.9 ± 18.2	0.05

[a]Continuous measures are summarized as means ± standard deviation (SD), and compared using the Yuen-Welch robust test.
[b]Lower scores represent better health.
[c]Higher scores represent better health.
GH, growth hormone; GHD, GH deficiency; GHI, GH insufficiency; QOL-AGHDA, Quality of Life–Assessment of GH Deficiency in Adults; SF-36, SF-36 Health Survey.

(Agha et al., 2004, 2005b; Aimaretti et al., 2004; Bondanelli et al., 2004; Kelly et al., 2000; Leal-Cerro et al., 2005; Lieberman et al., 2001; Popovic et al., 2004). Although there have been case reports of spontaneous recovery of chronic hypopituitarism, including resolution of isolated GHD (Agha et al., 2005a; Eiholzer et al., 1986; Iglesias et al., 1996), it appears that in the great majority of patients this deficit in somatotroph function is lasting.

Injury Characteristics Associated with Developing Growth Hormone Deficiency/ Growth Hormone Insufficiency

The eight patients with GHD/GHI were on average relatively severely injured, with a median GCS of 7.5; additionally, seven had diffuse brain swelling and seven had multiple hemorrhagic findings on acute CT. Although three of the patients had higher post-resuscitation GCS scores of 10, 11, and 15, all three of these patients had diffuse brain swelling and multiple hemorrhagic CT findings indicating a severe degree of parenchymal brain injury. Although prior studies have shown that hypopituitarism in general and GHD in particular, is most commonly associated with severe TBI, such endocrinopathies can also develop after milder head injuries (Benvenga et al., 2000; Bondanelli et al., 2004; Edwards and Clark, 1986; Kelly et al., 2000). Further research is needed to better define the patients most at risk for neuroendocrine deficits after head injury.

Neurobehavioral and Quality of Life Changes Associated with Growth Hormone Deficiency/Insufficiency

Of the NB/QOL battery performed on these TBI patients, depression, limitations due to physical health, energy and fatigue, pain, and general health were all more frequently affected in the GHD/GHI group than in the GH-sufficient patients. The median number of total NB deficits was also higher in the GHD/GHI group compared to the GH-sufficient group, but this did not reach statistical significance. Regarding the strong association of GHD/GHI with depression, it is notable that depression is a frequent finding in the moderate and severe TBI population with rates of 17–50% of patients in the chronic post-injury phase (Dikmen et al., 2004; Hellawell et al., 1999; Jorge et al., 2004; Kersel et al., 2001). Prior studies have also shown that patients with adult-onset GHD are more prone to NB deficits, particularly depression and QOL deficits (Abs et al., 2005; Arwert et al., 2005b; Blum et al., 2003; Deijen et al., 1996). Two recent reports also indicate that depression and poor QOL are improved by GH replacement in adult patients with GH deficiency (Mahajan et al., 2004; Mukherjee et al., 2005). Although one recent report by Popovic et al. (2004) did report an association between GHD and paranoid ideation in a TBI cohort, no relationship was seen between GHD and depression.

Given that the two patient groups in this study had similar degrees of TBI severity, these findings appear to support our original hypothesis that NB recovery and QOL may be limited in TBI patients as a result of GHD/GHI.

Whether GHD/GHI is acting as a primary factor or is acting synergistically with the residual effects of brain injury remains unclear. However, given the high frequency of diffuse brain swelling and a somewhat overall worse aggregate CT score in the GHD/GHI cohort, one alternative explanation for these findings is that increased depression and poor QOL in the GHD/GHI group is an epiphenomenon of the more severe brain injuries and secondary insults sustained in these patients. Due to the small sample size in this ongoing project, it is not possible to fully isolate the effects of the brain injury per se from that of untreated GHD/GHI. With accrual of additional patients, it may be possible to resolve this issue.

In summary, our findings (1) support the concept that isolated untreated GHD/GHI is associated with and may be in part responsible for persistent NB and QOL deficits in the chronic state after TBI; and (2) provide a rationale for conducting a randomized placebo-controlled trial to determine if GH-replacement therapy will alleviate or eliminate NB and QOL deficits in patients with GHD/GHI. Our own and other randomized placebo-controlled trials of GH therapy in TBI patients are underway.

Expanding Role of Growth Hormone and IGF-1 in the Central Nervous System

Numerous studies over the last decade lend support to the concept that the GH/IGF-1 system plays a key role in brain development, brain repair, and normal brain function. It is now clear that there are both GH and IGF-1 receptors in the brain and that their relative roles are quite different in the CNS. Whereas GH has been shown to be directly involved in vascular reactivity, vascular tone, and CNS repair processes after hypoxic injury (D'Ercole et al., 1996; Hana et al., 2002; Napoli et al., 2003; Saatman et al., 1997; Scheepens et al., 2000, 2001; Silha et al., 2005; Ye and D'Ercole, 1999; Ye et al., 2002; Zhong et al., 2005), IGF-1 appears to be an important factor in myelination, re-myelination, prevention of demyelination, and protection of oligodendrocytes from tumor necrosis factor–α induced apoptosis (D'Ercole et al., 1996; Hana et al., 2002; Napoli et al., 2003; Saatman et al., 1997; Scheepens et al., 2000, 2001; Silha et al., 2005; Ye and D'Ercole, 1999; Ye et al., 2002; Zhong et al., 2005). From these studies, it appears likely that GHD/GHI may constitute a potentially treatable, secondary post-injury condition that limits NB/QOL recovery due to low circulating levels of GH and/or IGF-1.

CONCLUSION

This analysis indicates that, following complicated mild, moderate, or severe TBI, approximately 18% of patients develop chronic GHD/GHI, which in the chronic state after injury is associated with depression and a poor QOL. Given that the GHD/GHI cohort had a similar degree of injury severity compared to GH-sufficient patients, NB and QOL differences between these two groups may be specifically related to untreated GHD/GHI. The impact of GH replacement therapy on NB function and QOL in TBI patients with GHD/GHI is being tested in a randomized placebo-controlled trial.

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REFERENCES

ABDU, T.A., ELHADD, T.A., NEARY, R., and CLAYTON, R.N. (1999). Comparison of the low-dose short synacthen test (1 microg), the conventional dose short synacthen test (250 microg), and the insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in patients with pituitary disease. J. Clin. Endocrinol. Metab. **84,** 838–843.

ABS, R., MATTSSON, A.F., BENGTSSON, B.K., et al. (2005). Isolated growth hormone (GH) deficiency in adult patients: baseline clinical characteristics and responses to GH replacement in comparison with hypopituitary patients. A sub-analysis of the KIMS database. Growth Horm. IGF Res. **15,** 349–359.

ADEKOYA, N., THURMAN, D.J., WHITE, D.D., and WEBB, K.W. (2002). Surveillance for traumatic brain injury deaths—United States, 1989–1998. MMWR Surveill. Summ. **51,** 1–14.

AGHA, A., ROGERS, B., SHERLOCK, M., et al. (2004). Anterior pituitary dysfunction in survivors of traumatic brain injury. J. Clin. Endocrinol. Metab. **89,** 4929–4936.

AGHA, A., RYAN, J., SHERLOCK, M., and THOMPSON, C.J. (2005a). Spontaneous recovery from posttraumatic hypopituitarism. Am. J. Phys. Med. Rehabil. **84,** 381–385.

AGHA, A., SHERLOCK, M., PHILLIPS, J., TORMEY, W., and THOMPSON, C.J. (2005b). The natural history of post-traumatic neurohypophysial dysfunction. Eur. J. Endocrinol. **152,** 371–377.

AIMARETTI, G., CORNELI, G., RAZZORE, P., et al. (1998). Comparison between insulin-induced hypoglycemia and growth hormone (GH)–releasing hormone + arginine as provocative tests for the diagnosis of GH deficiency in adults. J. Clin. Endocrinol. Metab. **83,** 1615–1618.

AIMARETTI, G., BELLONE, S., BAFFONI, C., et al. (2001). Short procedure of GHRH plus arginine test in clinical practice. Pituitary **4,** 129–134.

AIMARETTI, G., AMBROSIO, M.R., DI SOMMA, C., et al. (2004). Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury. Clin. Endocrinol. (Oxf.) **61,** 320–326.

AIMARETTI, G., AMBROSIO, M.R., DI SOMMA, C., et al. (2005). Residual pituitary function after brain injury–induced hypopituitarism: a prospective 12-month study. J. Clin. Endocrinol. Metab. **90,** 6085–6092.

ARIZA, M., MATARO, M., POCA, M.A., et al. (2004). Influence of extraneurological insults on ventricular enlargement and neuropsychological functioning after moderate and severe traumatic brain injury. J. Neurotrauma **21,** 864–876.

ARWERT, L.I., DEIJEN, J.B., MULLER, M., and DRENT, M.L. (2005a). Long-term growth hormone treatment preserves GH-induced memory and mood improvements: a 10-year follow-up study in GH-deficient adult men. Horm. Behav. **47,** 343–349.

ARWERT, L.I., DEIJEN, J.B., WITLOX, J., and DRENT, M.L. (2005b). The influence of growth hormone (GH) substitution on patient-reported outcomes and cognitive functions in GH-deficient patients: a meta-analysis. Growth Horm. IGF Res. **15,** 47–54.

ARWERT, L.I., VELTMAN, D.J., DEIJEN, J.B., LAMMERTSMA, A.A., JONKER, C., and DRENT, M.L. (2005c). Memory performance and the growth hormone/insulin-like growth factor axis in elderly: a positron emission tomography study. Neuroendocrinology **81,** 31–40.

BENGTSSON, B.A., EDEN, S., LONN, L., et al. (1993). Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. J. Clin. Endocrinol. Metab. **76,** 309–317.

BENVENGA, S., CAMPENNI, A., RUGGERI, R.M., and TRIMARCHI, F. (2000). Clinical review 113. Hypopituitarism secondary to head trauma. J. Clin. Endocrinol. Metab. **85,** 1353–1361.

BILLER, B.M., SAMUELS, M.H., ZAGAR, A., et al. (2002). Sensitivity and specificity of six tests for the diagnosis of adult GH deficiency. J. Clin. Endocrinol. Metab. **87,** 2067–2079.

BLUM, W.F., SHAVRIKOVA, E.P., EDWARDS, D.J., et al. (2003). Decreased quality of life in adult patients with growth hormone deficiency compared with general populations using the new, validated, self-weighted questionnaire, questions on life satisfaction hypopituitarism module. J. Clin. Endocrinol. Metab. **88,** 4158–4167.

BONDANELLI, M., DE MARINIS, L., AMBROSIO, M.R., et al. (2004). Occurrence of pituitary dysfunction following traumatic brain injury. J. Neurotrauma **21,** 685–696.

BORGARO, S.R., PRIGATANO, G.P., KWASNICA, C., and REXER, J.L. (2003). Cognitive and affective sequelae in complicated and uncomplicated mild traumatic brain injury. Brain Inj. **21,** 189–198.

BULLOCK, R., CHESNUT, R.M., CLIFTON, G., et al. (1996). Guidelines for the management of severe head injury. Brain Trauma Foundation. Eur. J. Emerg. Med. **3,** 109–127.

BUSCHKE, H., and FULD, P.A. (1974). Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology **24,** 1019–1025.

CASANUEVA, F.F., GHIGO, E., and POPOVIC, V. (2004). Hypopituitarism following traumatic brain injury (TBI): a guideline decalogue. J. Endocrinol. Invest. **27,** 793–795.

CEBALLOS, R. (1966). Pituitary changes in head trauma (analysis of 102 consecutive cases of head injury). Ala. J. Med. Sci. **3,** 185–198.

CHESNUT, R.M., MARSHALL, L.F., KLAUBER, M.R., et al. (1993a). The role of secondary brain injury in determining outcome from severe head injury. J. Trauma **34,** 216–222.

COHAN, P., WANG, C., McARTHUR, D.L., et al. (2005). Acute secondary adrenal insufficiency after traumatic brain injury: a prospective study. Crit. Care Med. **33,** 2358–2366.

D'ERCOLE, A.J., YE, P., CALIKOGLU, A.S., and GUTIERREZ-OSPINA, G. (1996). The role of the insulin-like growth factors in the central nervous system. Mol. Neurobiol. **13,** 227–255.

DANIEL, P.M. (1963). The pituitary gland and its blood supply. Sci. Basis Med. Annu. Rev. **84,** 83–98.

DANIEL, P.M., PRICHARD, M.M., and TREIP, C.S. (1959). Traumatic infarction of the anterior lobe of the pituitary gland. Lancet **2,** 927–931.

DEIJEN, J.B., DE BOER, H., BLOK, G.J., and VAN DER VEEN, E.A. (1996). Cognitive impairments and mood disturbances in growth hormone–deficient men. Psychoneuroendocrinology **21,** 313–322.

DEIJEN, J.B., DE BOER, H., and VAN DER VEEN, E.A. (1998). Cognitive changes during growth hormone replacement in adult men. Psychoneuroendocrinology **23,** 45–55.

DIKMEN, S.S., BOMBARDIER, C.H., MACHAMER, J.E., FANN, J.R., and TEMKIN, N.R. (2004). Natural history of depression in traumatic brain injury. Arch. Phys. Med. Rehabil. **85,** 1457–1464.

EDWARDS, O.M., and CLARK, J.D. (1986). Post-traumatic hypopituitarism. Six cases and a review of the literature. Medicine (Balt.) **65,** 281–290.

EIHOLZER, U., ZACHMANN, M., GNEHM, H.E., and PRADER, A. (1986). Recovery from post-traumatic anterior pituitary insufficiency. Eur. J. Pediatr. **145,** 128–130.

EISENBERG, H.M., GARY, H.E., JR., ALDRICH, E.F., et al. (1990). Initial CT findings in 753 patients with severe head injury. A report from the NIH Traumatic Coma Data Bank. J. Neurosurg. **73,** 688–698.

FELDT-RASMUSSEN, U., WILTON, P., and JONSSON, P. (2004). Aspects of growth hormone deficiency and replacement in elderly hypopituitary adults. Growth Horm. IGF Res. **14,** Suppl A, S51–S58.

FINDLER, M., CANTOR, J., HADDAD, L., GORDON, W., and ASHMAN, T. (2001). The reliability and validity of the SF-36 health survey questionnaire for use with individuals with traumatic brain injury. Brain Inj. **15,** 715–723.

GHARIB, H., COOK, D.M., SAENGER, P.H., et al. (2003). American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in adults and children—2003 update. Endocrinol. Pract. **9,** 64–76.

GHIGO, E., AIMARETTI, G., ARVAT, E., and CAMANNI, F. (2001). Growth hormone–releasing hormone combined with arginine or growth hormone secretagogues for the diagnosis of growth hormone deficiency in adults. Endocrine **15,** 29–38.

GHIGO, E., MASEL, B., AIMARETTI, G., et al. (2005). Consensus guidelines on screening for hypopituitarism following traumatic brain injury. Brain Inj. **19,** 711–724.

GIUSTI, M., MEINERI, I., MALAGAMBA, D., et al. (1998). Impact of recombinant human growth hormone treatment on psychological profiles in hypopituitary patients with adult-onset growth hormone deficiency. Eur. J. Clin. Invest. **28,** 13–19.

GLENN, T.C., KELLY, D.F., BOSCARDIN, W.J., et al. (2003). Energy dysfunction as a predictor of outcome after moderate or severe head injury: indices of oxygen, glucose, and lactate metabolism. J. Cereb. Blood Flow Metab. **23,** 1239–1250.

GOTHERSTROM, G., SVENSSON, J., KORANYI, J., et al. (2001). A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. J. Clin. Endocrinol. Metab. **86,** 4657–4665.

HANA, V., PRAZNY, M., MAREK, J., SKRHA, J., and JUSTOVA, V. (2002). Reduced microvascular perfusion and reactivity in adult GH-deficient patients is restored by GH replacement. Eur. J. Endocrinol. **147,** 333–337.

HELLAWELL, D.J., TAYLOR, R.T., and PENTLAND, B. (1999). Cognitive and psychosocial outcome following moderate or severe traumatic brain injury. Brain Inj. **13,** 489–504.

HOFFMAN, D.M., O'SULLIVAN, A.J., BAXTER, R.C., and HO, K.K. (1994). Diagnosis of growth-hormone deficiency in adults. Lancet **343,** 1064–1068.

IGLESIAS, P., GOMEZ-PAN, A., and DIEZ, J.J. (1996). Spontaneous recovery from post-traumatic hypopituitarism. J. Endocrinol. Invest. **19,** 320–323.

JENNETT, B., and BOND, M. (1975). Assessment of outcome after severe brain damage. Lancet **1,** 480–484.

JIANG, J.Y., GAO, G.Y., LI, W.P., YU, M.K., and ZHU, C. (2002). Early indicators of prognosis in 846 cases of severe traumatic brain injury. J. Neurotrauma **19,** 869–874.

JORGE, R.E., ROBINSON, R.G., MOSER, D., TATENO, A., CRESPO-FACORRO, B., and ARNDT, S. (2004). Major depression following traumatic brain injury. Arch. Gen. Psychiatry **61,** 42–50.

KELLY, D.F., GONZALO, I.T., COHAN, P., BERMAN, N., SWERDLOFF, R., and WANG, C. (2000). Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a preliminary report. J. Neurosurg. **93,** 743–752.

KERSEL, D.A., MARSH, N.V., HAVILL, J.H., and SLEIGH, J.W. (2001). Psychosocial functioning during the year following severe traumatic brain injury. Brain Inj. **15,** 683–696.

KESELMAN, H.J., OTHMAN, A.R., WILCOX, R.R., and FRADETTE, K. (2004). The new and improved two-sample *t* test. Psychol. Sci. **15,** 47–51.

KOLTOWSKA-HAGGSTROM, M., HENNESSY, S., MATTSSON, A.F., MONSON, J.P., and KIND, P. (2005). Quality of Life–Assessment of Growth Hormone Deficiency in Adults (QOL-AGHDA): comparison of normative reference data for the general population of England and Wales with results for adult hypopituitary patients with growth hormone deficiency. Horm. Res. **64,** 46–54.

KORNBLUM, R.N., and FISHER, R.S. (1969). Pituitary lesions in craniocerebral injuries. Arch. Pathol. **88,** 242–248.

KRAUS, J.F., and McARTHUR, D.L. (1996). Epidemiologic aspects of brain injury. Neurol. Clin. **14,** 435–450.

KRAUS, J.F., RICE, T.M., PEEK-ASA, C., and McARTHUR, D.L. (2003). Facial trauma and the risk of intracranial injury in motorcycle riders. Ann. Emerg. Med. **41,** 18–26.

LEAL-CERRO, A., FLORES, J.M., RINCON, M., et al. (2005). Prevalence of hypopituitarism and growth hormone deficiency in adults long-term after severe traumatic brain injury. Clin. Endocrinol. (Oxf.) **62,** 525–532.

LEVIN, H.S., GARY, H.E., JR., EISENBERG, H.M., et al. (1990). Neurobehavioral outcome 1 year after severe head injury. Experience of the Traumatic Coma Data Bank. J. Neurosurg. **73,** 699–709.

LIEBERMAN, S.A., OBEROI, A.L., GILKISON, C.R., MASEL, B.E., and URBAN, R.J. (2001). Prevalence of neuroendocrine dysfunction in patients recovering from traumatic brain injury. J. Clin. Endocrinol. Metab. **86,** 2752–2756.

MACKENZIE, E.J., McCARTHY, M.L., DITUNNO, J.F., et al. (2002). Using the SF-36 for characterizing outcome after multiple trauma involving head injury. J. Trauma **52,** 527–534.

MAHAJAN, T., CROWN, A., CHECKLEY, S., FARMER, A., and LIGHTMAN, S. (2004). Atypical depression in growth hormone–deficient adults, and the beneficial effects of growth hormone treatment on depression and quality of life. Eur. J. Endocrinol. **151,** 325–332.

MARMAROU, A., ANDERSON, R., and WARD, J. (1991). Impact of ICP instability and hypotension on outcome in patients with severe head trauma. J. Neurosurg. **75,** S59–S66.

MARSHALL, L., GAUTILLE, T., and KLAUBER, M. (1991a). The outcome of severe closed head injury. J. Neurosurg. **75,** A28–A36.

MARSHALL, L., MARSHALL, S., and KLAUBER, M. (1991b). A new classification of head injury based on computerized tomography. J. Neurosurg. **75,** S14–S20.

McCAULEY, S.R., HANNAY, H.J., and SWANK, P.R. (2001a). Use of the Disability Rating Scale Recovery curve as a predictor of psychosocial outcome following closed-head injury. J. Int. Neuropsychol. Soc. **7,** 457–467.

McCAULEY, S.R., LEVIN, H.S., VANIER, M., et al. (2001b). The Neurobehavioral Rating Scale–Revised: sensitivity and validity in closed head injury assessment. J. Neurol. Neurosurg. Psychiatry **71,** 643–651.

McGAULEY, G.A., CUNEO, R.C., SALOMON, F., and SONKSEN, P.H. (1990). Psychological well-being before and after growth hormone treatment in adults with growth hormone deficiency. Horm. Res. **33,** Suppl 4, 52–54.

McKENNA, S.P., DOWARD, L.C., ALONSO, J., et al. (1999). The QoL-AGHDA: an instrument for the assessment of quality of life in adults with growth hormone deficiency. Qual. Life Res. **8,** 373–383.

MILLER, J.D., SWEET, R.C., NARAYAN, R., and BECKER, D.P. (1978). Early insults to the injured brain. JAMA **240,** 439–442.

MUKHERJEE, A., TOLHURST-CLEAVER, S., RYDER, W.D., SMETHURST, L., and SHALET, S.M. (2005). The characteristics of quality of life impairment in adult growth hormone (GH)–deficient survivors of cancer and their response to GH replacement therapy. J. Clin. Endocrinol. Metab. **90,** 1542–1549.

NAPOLI, R., GUARDASOLE, V., ANGELINI, V., et al. (2003). Acute effects of growth hormone on vascular function in human subjects. J. Clin. Endocrinol. Metab. **88,** 2817–2820.

NARAYAN, R.K., MICHEL, M.E., ANSELL, B., et al. (2002). Clinical trials in head injury. J. Neurotrauma **19,** 503–557.

NIH. (1999). Consensus conference. Rehabilitation of persons with traumatic brain injury. NIH Consensus Development Panel on Rehabilitation of Persons with Traumatic Brain Injury. JAMA **282,** 974–983.

POPOVIC, V., PEKIC, S., PAVLOVIC, D., et al. (2004). Hypopituitarism as a consequence of traumatic brain injury (TBI) and its possible relation with cognitive disabilities and mental distress. J. Endocrinol. Invest. **27,** 1048–1054.

QU, X.D., GAW GONZALO, I.T., AL SAYED, M.Y., et al. (2005). Influence of body mass index and gender on growth hormone (GH) responses to GH-releasing hormone plus arginine and insulin tolerance tests. J. Clin. Endocrinol. Metab. **90,** 1563–1569.

RADLOFF, L.S. (1977). The CES-D Scale: a self-report depression scale for research in the general population. Appl. Psychol. Measurement **1,** 385–401.

REY, A. (1941). [L'examen psychologique dans les cas d'encephalopathie traumatique]. Arch. Psychol. **28,** 286–340.

ROLLERO, A., MURIALDO, G., FONZI, S., et al. (1998). Relationship between cognitive function, growth hormone and insulin-like growth factor–I plasma levels in aged subjects. Neuropsychobiology **38,** 73–79.

ROSEN, T., WILHELMSEN, L., LANDIN-WILHELMSEN, K., LAPPAS, G., and BENGTSSON, B.A. (1997). Increased fracture frequency in adult patients with hypopituitarism and GH deficiency. Eur. J. Endocrinol. **137,** 240–245.

SAATMAN, K.E., CONTRERAS, P.C., SMITH, D.H., et al. (1997). Insulin-like growth factor–1 (IGF-1) improves both neurological motor and cognitive outcome following experimental brain injury. Exp. Neurol. **147,** 418–427.

SARRAFZADEH, A.S., PELTONEN, E.E., KAISERS, U., KUCHLER, I., LANKSCH, W.R., and UNTERBERG, A.W. (2001). Secondary insults in severe head injury—do multiply injured patients do worse? Crit. Care Med. **29,** 1116–1123.

SCHEEPENS, A., SIRIMANNE, E.S., BREIER, B.H., CLARK, R.G., GLUCKMAN, P.D., and WILLIAMS, C.E. (2001). Growth hormone as a neuronal rescue factor during recovery from CNS injury. Neuroscience **104,** 677–687.

SCHEEPENS, A., WILLIAMS, C.E., BREIER, B.H., GUAN, J., and GLUCKMAN, P.D. (2000). A role for the somatotropic axis in neural development, injury and disease. J. Pediatr. Endocrinol. Metab. **13,** Suppl 6, 1483–1491.

SCHNEIDER, M., SCHNEIDER, H.J., and STALLA, G.K. (2005). Anterior pituitary hormone abnormalities following traumatic brain injury. J. Neurotrauma **22,** 937–946.

SILHA, J.V., KRSEK, M., HANA, V., et al. (2005). The effects of growth hormone status on circulating levels of vascular growth factors. Clin. Endocrinol. (Oxf.) **63,** 79–86.

SMITH, A. (1973). *Symbol Digit Modalities Test (Manual).* Western Psychological Services: Los Angeles.

SOARES, C.N., MUSOLINO, N.R., CUNHA NETO, M., et al. (1999). Impact of recombinant human growth hormone (RH-GH) treatment on psychiatric, neuropsychological and clinical profiles of GH-deficient adults. A placebo-controlled trial. Arq. Neuropsiquiatr. **57,** 182–189.

SVENSSON, J., MATTSSON, A., ROSEN, T., et al. (2004). Three-years of growth hormone (GH) replacement therapy in GH-deficient adults: effects on quality of life, patient-reported outcomes and healthcare consumption. Growth Horm. IGF Res. **14,** 207–215.

TEASDALE, G., and JENNETT, B. (1974). Assessment of coma and impaired consciousness. A practical scale. Lancet **2,** 81–84.

TEASDALE, G.M., PETTIGREW, L.E., WILSON, J.T., MURRAY, G., and JENNETT, B. (1998). Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow Outcome Scale. J. Neurotrauma **15,** 587–597.

TOMEI, G., SGANZERLA, E., SPAGNOLI, D., et al. (1991). Posttraumatic diffuse cerebral lesions. Relationship between clinical course, CT findings and ICP. J. Neurosurg. Sci. **35,** 61–75.

URBAN, R.J., HARRIS, P., and MASEL, B. (2005). Anterior hypopituitarism following traumatic brain injury. Brain Inj. **19,** 349–358.

VAN DAM, P.S., ALEMAN, A., DE VRIES, W.R., et al. (2000). Growth hormone, insulin-like growth factor–I and cognitive function in adults. Growth Horm. IGF Res. **10,** Suppl B, S69–S73.

WAGNER, A.K., HAMMOND, F.M., SASSER, H.C., and WIERCISIEWSKI, D. (2002). Return to productive activity after traumatic brain injury: relationship with measures of

disability, handicap, and community integration. Arch. Phys. Med. Rehabil. **83,** 107–114.

WARE, J.E., JR., and SHERBOURNE, C.D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med. Care **30,** 473–483.

WILCOX, R.R. (1997). *Introduction to Robust Estimation and Hypothesis Testing.* Academic Press: New York.

WILSON, J.T., PETTIGREW, L.E., and TEASDALE, G.M. (1998). Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J. Neurotrauma **15,** 573–585.

WILSON, J.T., PETTIGREW, L.E., and TEASDALE, G.M. (2000). Emotional and cognitive consequences of head injury in relation to the Glasgow Outcome Scale. J. Neurol. Neurosurg. Psychiatry **69,** 204–209.

WIREN, L., BENGTSSON, B.A., and JOHANNSSON, G. (1998). Beneficial effects of long-term GH replacement therapy on quality of life in adults with GH deficiency. Clin. Endocrinol. (Oxf.) **48,** 613–620.

YE, P., and D'ERCOLE, A.J. (1999). Insulin-like growth factor–I protects oligodendrocytes from tumor necrosis factor–alpha–induced injury. Endocrinology **140,** 3063–3072.

YE, P., LI, L., RICHARDS, R.G., DIAUGUSTINE, R.P., and D'ERCOLE, A.J. (2002). Myelination is altered in insulin-like growth factor–I null mutant mice. J. Neurosci. **22,** 6041–6051.

YUEN, K.K. (1974). The two-sample trimmed *t* for unequal population variances. Biometrika **61,** 165–170.

ZARKOVIC, M., CIRIC, J., STOJANOVIC, M., et al. (1999). Optimizing the diagnostic criteria for standard (250-microg) and low-dose (1-microg) adrenocorticotropin tests in the assessment of adrenal function. J. Clin. Endocrinol. Metab. **84,** 3170–3173.

ZHONG, J., DENG, J., PHAN, J., et al. (2005). Insulin-like growth factor–I protects granule neurons from apoptosis and improves ataxia in weaver mice. J. Neurosci. Res. **80,** 481–490.

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4. M. Klose, U. Feldt-Rasmussen. 2008. Does the type and severity of brain injury predict hypothalamo–pituitary dysfunction? Does post-traumatic hypopituitarism predict worse outcome?. *Pituitary* **11**:3, 255-261. [CrossRef]
5. Joshua R. Dusick, Christina Wang, Pejman Cohan, Ronald Swerdloff, Daniel F. Kelly. 2008. Chapter 1: pathophysiology of hypopituitarism in the setting of brain injury. *Pituitary* . [CrossRef]
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